Remarks

Claims 15-18 and 20-25 were pending in the subject application. By this amendment, claim 15 has been amended and claim 16 has been cancelled. The amendment to claim 15 to recite that the present method is useful with respect to "pneumonia, urinary tract infection and/or sepsis" is supported at, for example, page 1, paragraph 1 of the application as filed. Support for the phrase "to reduce lethality and morbidity" can also be found at, for example, page 1, paragraph 1 of the specification. The recitation that the at least one anti-infective agent "comprises at least one antibiotic in a pharmaceutical preparation" was in original claim 16. The recitation that the anti-infective therapy is started within 72 hours following the stroke is supported at, for example, page 5, paragraph 5 of the application as filed. No new matter has been added by these amendments. Accordingly, claims 15, 17, 18 and 20-25 are currently before the Examiner for consideration. Favorable consideration is respectfully requested.

The amendments presented herein have been made to lend greater clarity to the claimed subject matter and to expedite prosecution of the subject application to completion. These amendments should not be construed as an indication of the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 15-18 and 20-25 have been rejected under 35 U.S.C. §112, first paragraph. The applicants respectfully traverse this ground for rejection because the skilled artisan, having the benefit of the applicants' disclosure could readily, and without undue experimentation, practice the subject invention as now claimed.

It is important to bear in mind that, for an invention to be enabled under the first paragraph of §112, the specification need only teach a person of ordinary skill in the art "how to make" and "how to use" the invention. The subject application provides ample guidance to meet this standard for the claims now presented for examination.

Please note that claim 15 has been amended herein to recite therapy for certain specific pathological conditions, i.e. pneumonia, urinary tract infections, and sepsis. Advantageously, lethality and morbidity arising from these infections can be reduced according to the subject

invention by administering to a patient an anti-infective agent or immunomodulating agent as described in the present application.

As noted above, amended claim 15 now explicitly states that the method of the invention reduces lethality and morbidity of a patient who has suffered an acute stroke. Thus, the method of the present invention is particularly advantageous because it results in an improvement in the overall outcome of a patient who has suffered an acute stroke.

Still further, amended claim 15 now states that, in the present method, at least one antibiotic in a pharmaceutical preparation is administered to the patient. From the examples provided in the present application, it is evident that each of the anti-infective agents and immunomodulating agents described in the application can by used in the present method to reduce the development of post-stroke infections as well as mortality. Specifically, in the examples the anti-infective agents mezlocillin and sulbactam (examples 2A and 3A), imipenem and cilastatin (example 4A), moxifloxacin (example 5A) as well as the immunomodulating agents propranolol (examples 2B and 4B) and IFN-γ (example 3B) as well as beta-blockers were used.

Furthermore, attached herewith is an article authored by the current inventors in which it is demonstrated in a randomized controlled trial that the method of the invention can be practiced using moxifloxacin as an anti-infective agent. The article was published in a peer-reviewed international scientific journal. Having been successful with this agent, as well as those that are exemplified in the specification, there is no basis for doubting the ability to use other agents in the claimed method.

In addition, the feature newly added to claim 15, that the anti-infective therapy is started within 72 hours following the stroke, provides further guidance to a person of skill in the art as to how to practice the present method.

The Office Action states that it cannot be predicted that all anti-infective agents will prevent all infections of the urinary tract, the lungs and the blood (sepsis), because organisms causing these infections may mutate and become resistant to certain medicinal agents. First, the potential for such problems is generally known to a person of skill in the art and is taken into account when treating a patient. Further, the possibility of resistant microbes by no means renders the claims non-enabled.

It should be noted that the requirement for some experimentation and/or screening does not necessarily make a claim non-enabled. "Enablement is not precluded by the necessity for some

experimentation such as routine screening. . . A considerable amount of experimentation is permissible, if it is merely routine . . ." (emphasis added). *In re Wands,* 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

The mere possibility that certain microorganisms might be resistant to a particular drug does not in any way negate the general applicability of the method as claimed; the kind of "experimentation" necessary to practice this invention is routine to a skilled artisan. Furthermore, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled (MPEP 2164.08(b)).

As noted above, for an invention to be enabled under the first paragraph of §112, the specification need only teach a person of ordinary skill in the art "how to make" and "how to use" the invention. It is further noted that the sheer number of compounds or embodiments that may fall within the scope of a claim is not determinative of the enablement of the specification. See, e.g., *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976), where the court observed that a large but finite list of materials, in combination with a teaching of how to carry out the invention, was enabling for purposes of §112.

The applicants are cognizant of the duty under §112, first paragraph, to provide sufficient teaching in the specification to enable one skilled in the art to practice the invention as claimed without undue experimentation. For the reasons set forth above, the applicants believe that they have fulfilled the requirements of 35 USC §112. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 15-18 and 20-25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fong (*The Journal of Infectious Diseases,* 2000, Vol. 181, Suppl. 3, pp. S514-S518) in view of Vlasselaer *et al.* (US 2001/0043906). The applicants respectfully traverse this ground for rejection because the cited references, taken either alone or in combination, do not disclose or suggest the claimed invention.

It is well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant. *KSR International Co. v. Teleflex Inc.*, 550 U.S.

___ (2007). Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." *Id.*

Claim 15 has been amended herein to recite that the present method is for reducing lethality and morbidity of a patient who has suffered an acute stroke wherein the anti-infective therapy is started within 72 hours following the stroke. Neither Fong nor Vlasselaer *et al.* provide any hints that such anti-infective therapy would lead to a reduction of lethality and morbidity of a patient, nor do they suggest a time window within which the anti-infective therapy can be started. The current time window of up to 72 hours after the occurrence of the acute stroke is a surprisingly long time window, and one which is not suggested by the prior art.

Attached herewith is a copy of the publication "Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008" which on page 482 states that a preventive therapy after stroke using antibiotics is not recommended. Thus, the art as a whole actually contained disclosures that taught away from the current invention.

An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

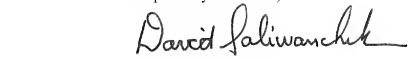
In the current case, the cited references, either taken alone or in combination do not disclose or suggest the applicants' advantageous method. Therefore, the applicants respectfully request reconsideration and withdrawal of the obviousness rejection under 35 U.S.C. §103 based on Fong in view of Vlasselaer *et al.*

In view of the foregoing remarks, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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DRS/la

Attachments: Copy of "Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008"
Copy of "Preventive Antibacterial Therapy in Acute Ischemic Stroke: A Randomized Controlled Trial"

Consensus Paper

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Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008

The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee

Key Words
Stroke prevention · Educational measures · Stroke Unit · Imaging · Acute treatment · Rehabilitation

Abstract
This article represents the update of the European Stroke Initiative Recommendations for Stroke Management. These guidelines cover both ischaemic stroke and transient ischaemic attacks, which are now considered to be a single entity. The article covers referral and emergency management, Stroke Unit service, diagnostics, primary and secondary prevention, general stroke treatment, specific treatment including acute management, management of complications, and rehabilitation.

Foreword

This article represents the update of the European Stroke Initiative (EUSI) Recommendations for Stroke Management, which were first published in this journal in 2000 [1, 2], and subsequently translated into a number of languages including Spanish, Portuguese, Italian, German, Greek, Turkish, Lithuanian, Polish, Russian and Mandarin Chinese. The first update of the recommendations was published in 2003 [2]. In 2006, the EUSI decided that a larger group of authors should prepare the next update. In the meantime, a new European Stroke Society, the European Stroke Organisation (ESO), was established and took over the task of updating the guidelines. Accordingly, the new recommendations have been prepared by members of both the former EUSI Recommendations Writing Committee and the ESO (see appendix). The members of the Writing Group met in Heidelberg, Germany for 3 days in December 2007 to finalize the new

The ESO Writing Committee: Peter A. Ringleb, Heidelberg, Germany; Marie-Germaine Bousser, Paris, France; Gary Ford, Newcastle, UK; Philip Bath, Nottingham, UK; Michael Brainin, Krems, Austria; Valeria Caso, Perugia, Italy; Álvaro Cervera, Barcelona, Spain; Angel Chamorro, Barcelona, Spain; Charlotte Cordonnier, Lille, France; László Csiba, Debrecen, Hungary; Antoni Davalos, Barcelona, Spain; Hans-Christoph Diener, Essen, Germany; José Ferro, Lisbon, Portugal; Werner Hacke, Heidelberg, Germany; Michael Hennerici, Mannheim, Germany; Markku Kaste, Helsinki, Finland; Peter Langhorne, Glasgow, UK; Kennedy Lees, Glasgow, UK; Didier Leys, Lille, France; Jan Lodder, Maastricht, The Netherlands; Hugh S. Markus, London, UK; Jean-Louis Mas, Paris, France; Heinrich P. Mattle, Bern, Switzerland; Keith Muir, Glasgow, UK; Bo Norrving, Lund, Sweden; Victor Obach, Barcelona, Spain; Stefano Paolucci, Rome, Italy; E. Bernd Ringelstein, Münster, Germany; Peter D. Schellinger, Erlangen, Germany; Juhani Sivenius, Kuopio, Finland; Veronika Skvortsova, Moscow, Russia; Katharina Stibrant Sunnerhagen, Göteborg, Sweden; Lars Thomassen, Bergen, Norway; Danilo Toni, Rome, Italy; Rüdiger von Kummer, Dresden, Germany; Nils Gunnar Wahlgren, Stockholm, Sweden; Marion F. Walker, Nottingham, UK; Joanna Wardlaw, Edinburgh, UK.

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Table 1. Classification of evidence for diagnostic and for therapeutic measures (from Brainin et al. [582])

	Evidence classification scheme for a diagnostic measure	Evidence classification scheme for a therapeutic intervention
Class I	A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy	An adequately powered, prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: a randomization concealment b primary outcome(s) is/are clearly defined c exclusion/inclusion criteria are clearly defined d adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias e relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criterion a–e
Class III	Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion	Evidence from uncontrolled studies, case series, case reports, or expert opinion

recommendations. The members of the Writing Committee were assigned to six groups covering different topics. Each group was co-chaired by two colleagues, and included up to five further experts. In order to avoid bias or conflict of interest, none of the chairs had major involvement in clinical trials or studies discussed in their respective group.

These guidelines cover both ischaemic stroke and transient ischaemic attacks (TIAs), which are now considered to be a single entity. If recommendations differ for the two conditions, this will be explicitly mentioned; otherwise the recommendations are valid for both conditions. Separate guidelines exist or are being prepared for intracerebral haemorrhage [3] and subarachnoid haemorrhage. The classes of evidence and levels of recommendations used in these guidelines are defined according to the criteria of the European Federation of Neurological Societies (table 1, 2). The article covers referral and emergency management, Stroke Unit service, diagnostics, primary and secondary prevention, general stroke treatment, specific treatment including acute management, management of complications, and rehabilitation.

Changes in the guidelines necessitated by new evidence will be continuously incorporated in the on-line version that can be found on the ESO website (www.eso-stroke.org). The reader is advised to check the online version when making important treatment decisions.

Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide [4]. Large differences in incidence, prevalence and mortality have been noted between Eastern and Western Europe. This has been attributed to differences in risk factors, with higher levels of hypertension and other risk factors resulting in more severe stroke in Eastern Europe [5]. Notable regional variations have also been found within Western Europe. Stroke is the most important cause of morbidity and long-term disability in

ESO Executive Committee and
ESO Writing Committee

Europe, and demographic changes will result in an increase in both incidence and prevalence. It is also the second most common cause of dementia, the most frequent cause of epilepsy in the elderly, and a frequent cause of depression [6, 7].

Many guidelines and recommendations for stroke management or specific aspects of stroke care have been published during the last decade [2, 8–18]. Most recently, the updated Helsingborg Declaration focused on standards of stroke care and research needs in Europe [19]. In the future, the global harmonization of stroke guidelines will be the focus of the World Stroke Organisation, supported by the ESO and other national and regional stroke societies.

Table 2. Definitions for levels of recommendation (from Brainin et al. [582])

Level A	Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class I study or at least two consistent, convincing Class II studies
Level B	Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class II study or overwhelming Class III evidence
Level C	Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least two Class III studies
GCP points	Recommended best practice based on the experience of the guideline development group. Usually based on Class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers

Public Awareness and Education

Recommendations
- Educational programmes to increase awareness of stroke at the population level are recommended (Class II, Level B).
- Educational programmes to increase stroke awareness among professionals (paramedics/emergency physicians) are recommended (Class II, Level B).

The 'time is brain' concept means that treatment of stroke should be considered as an emergency. Thus, avoiding delay should be the major aim in the prehospital phase of acute stroke care. This has far-reaching implications in terms of recognition of signs and symptoms of stroke by the patient or by relatives or bystanders, the nature of first medical contact, and the means of transportation to hospital.

Delays during acute stroke management have been identified at different levels [20]:
- at the population level, due to failure to recognize the symptoms of stroke and contact emergency services
- at the level of the emergency services and emergency physicians, due to a failure to prioritize transport of stroke patients
- at the hospital level, due to delays in neuroimaging and inefficient in-hospital care.

A large amount of time is lost outside the hospital [21]: for stroke patients at a Portuguese university hospital this accounted for 82% of the delay in treatment [22]. Studies that identify demographic, social, cultural, behavioural and clinical factors associated with longer prehospital time may provide targets for educational campaigns [23, 24].

The interval from symptom onset to first call for medical help is the predominant part of prehospital delay [25–28]. Major reasons for delayed contact include lack of awareness of stroke symptoms and recognition of their severity, but also denial of the disease and the hope that symptoms would resolve. This suggests that educating the population to recognize stroke symptoms, and changing people's attitudes to acute stroke, may reduce the delay from stroke onset to emergency medical service (EMS) involvement.

Medical attention is rarely sought by the patient: in many cases contact is initially made by a family member [28–30]. Information and educational initiatives should therefore be directed both to persons at high risk of stroke and also to those around them.

Stroke awareness depends on demographic and sociocultural factors, and on personal medical knowledge. Knowledge of stroke warning signs varies considerably, depending on the symptoms, and is dependent on the way questions are asked (e.g. open-ended or multiple-choice questions [31, 32]).

While most people agree that stroke is an emergency, and that they would seek medical help immediately, in reality only up to 50% call EMS. In many cases, the first contact is with a family member or with a general practitioner; in some studies between 45% and 48% of patients were referred via a general practitioner [29, 33–36].

Most studies show that only approximately 33–50% of patients recognize their own symptoms as stroke. There are considerable discrepancies between theoretical knowledge of stroke and the reaction in case of an acute

stroke. Some studies have shown that patients with better knowledge of stroke symptoms do not always arrive earlier at hospital.

The most frequently used sources of stroke information are mass media [37–39], and friends and relatives who have knowledge of stroke; only rarely is information derived from general practitioners or books [40–44]. The sources accessed vary with age: older people more often obtain information from health campaigns or their general practitioner, whereas younger people gain more information from TV [38–40].

Interventional studies have measured the effect of education on stroke knowledge. Eight non-randomized studies measured the impact of educational measures on prehospital time delay or thrombolysis use [45–52]. In six studies, the intervention was a combined educational programme directed at the public, paramedics and health professionals, while in two studies education was directed only to the population. Only the TLL Temple Foundation Stroke Project included a concurrent control group [50, 51]. All studies had a pre-post design. Thrombolysis usage increased after education in the intervention group of the TLL study, but only for up to 6 months after intervention ended [51]. This suggests that public education has to be maintained to sustain stroke awareness in the population.

Education should also be directed to paramedics and emergency department (ED) staff to improve the accuracy of stroke identification and speed up transfer to the hospital [53]. Education of paramedics increases stroke knowledge, clinical and communication skills and decreases prehospital delays [54].

Educating medical students in basic stroke knowledge during their first year at medical school has been shown to be associated with a high degree of knowledge retention [55]. The value of postgraduate training is universally acknowledged, but training programmes for stroke specialists are still heterogeneous throughout Europe. To overcome such heterogeneity and to increase the number of specialists available for stroke care, some countries (e.g. France, UK) have developed and implemented national curricula. In contrast, other countries rely on training specialization within neurology training programmes. With a view towards harmonization of training, a European Masters' Programme for Stroke Medicine (http://www.donau-uni.ac.at/en/studium/stroke-medicine/index.php), and annual Stroke Summer Schools (http://www.eso-stroke.org), have been established.

Referral and Patient Transfer

Recommendations

- Immediate EMS contact and priority EMS dispatch are recommended (Class II, Level B)
- Priority transport with advance notification to the receiving hospital (outside and inside hospital) is recommended (Class III, Level B)
- It is recommended that suspected stroke victims should be transported without delay to the nearest medical centre with a stroke unit that can provide ultra-early treatment (Class III, Level B)
- It is recommended that dispatchers and ambulance personnel be trained to recognise stroke using simple instruments such as the Face-Arm-Speech Test (Class IV, Good Clinical Practice – GCP)
- Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital are recommended (Class III, Level B)
- It is recommended that in remote or rural areas helicopter transfer should be considered in order to improve access to treatment (Class II, Level C)
- It is recommended that in remote or rural areas telemedicine should be considered in order to improve access to treatment (Class II, Level B)
- It is recommended that patients with suspected TIA be referred without delay to a TIA clinic or to a medical centre with a stroke unit that can provide expert evaluation and immediate treatment (Class III, Level B)

Successful care of the acute stroke victim begins with the recognition by both the public and health professionals [56] that stroke is an emergency, like acute myocardial infarction (MI) or trauma. However, in practice the majority of ischaemic stroke patients do not receive recombinant tissue plasminogen activator (rtPA) because they do not reach the hospital soon enough [22, 36, 57, 58]. Emergency care of the acute stroke victim depends on a four-step chain:

- rapid recognition of, and reaction to, stroke signs and TIAs
- immediate EMS contact and priority EMS dispatch
- priority transport with notification of the receiving hospital
- immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, and administration of appropriate treatments at the receiving hospital.

Once stroke symptoms are suspected, patients or their proxies should call EMS. The EMS system should have an electronic validated algorithm of questions to diagnose stroke during the phone interview [33, 59]. The ambulance dispatchers and paramedics should be able to di-

agnose stroke using simple instruments such as the Face-Arm-Speech Test [60]. They should also be able to identify and provide appropriate help for patients who need urgent care because of early complications or comorbidities of stroke, such as impaired consciousness, seizures, vomiting, or haemodynamic instability.

Suspected stroke victims should be transported without delay to the nearest medical centre with a stroke unit that can provide ultra-early treatment. Patients with onset of stroke symptoms within 3 h should be given priority in evaluation and transportation [20]. In each community, a network of stroke units or, if stroke units are not yet available, a network of medical centres providing organized acute stroke care should be implemented and publicized to the general population, health professionals and the emergency transport systems [61, 62].

If a doctor receives a call or consultation from a patient with suspected stroke, he or she should recommend or arrange transportation, preferably through the EMS system, to the nearest hospital with a stroke unit providing organized acute stroke care and ultra-early treatment. Ambulance dispatchers should inform the stroke unit and describe the patient's clinical status. Proxies who can describe symptom onset or the patient's medical history should accompany the patient.

Few intervention studies have examined the impact of decreasing the delay from symptom onset to arrival at the hospital and making ultra-early treatment accessible for a larger proportion of patients. Most such studies have used a before-and-after intervention design, were neither randomized nor masked with respect to intervention or evaluation of outcome, and lacked concurrent controls [23, 53]. The types of interventions included education and training programmes, helicopter transfer, telemedicine and reorganisation of pre-hospital and in-hospital protocols for acute stroke patients.

Direct presentation to the ED via ambulance or EMS transportation is the fastest way of referral [28, 53, 63–65]. Helicopter transport can reduce the time between referral and hospital arrival [66, 67], and also promotes access to thrombolytic therapy in remote and rural areas [68]. In mixed rural and urban areas, air and ground distances can be compared using simple rules [69]. No studies have compared air and ground transport specifically in stroke patients. In one study, predominantly in trauma patients, ground ambulances provided shorter arrival times at distances less than 10 miles (≅16 km) from the hospital; even with only short delays in despatching air transport, air was faster only for distances longer than 45 miles (≅72 km) [70]. One economic study showed that helicopter transfer of patients with suspected acute ischaemic stroke for potential thrombolysis is cost-effective [71].

Telemedicine using a bidirectional video-conferencing equipment to provide health services or assist health care personnel at distant sites is a feasible, valid and reliable means of facilitating thrombolysis delivery to patients in distant or rural hospitals, where timely air or ground transportation is not feasible. The quality of treatment, complication rates, and short- and long-term outcomes are similar for acute stroke patients treated with rtPA via a telemedicine consultation at local hospitals and those treated in academic centres [72–81].

Activation of the stroke code as a special infrastructure with immediate calling of a stroke neurologist at a stroke unit and priority transfer of the patients to this centre is effective in increasing the percentage of patients treated with thrombolysis, and also in shortening pre-hospital delays [82, 83].

Recent community and hospital-based studies demonstrated a high risk of stroke immediately after a TIA [6, 84]. Observational studies showed that urgent evaluation at a TIA clinic and immediate initiation of treatment reduces stroke risk after TIA [85, 86]. This underlines the need for urgent referral of TIA for expert evaluation and immediate treatment.

Emergency Management

Recommendations

- Organisation of pre-hospital and in-hospital pathways and systems for acute stroke patients is recommended (Class III, Level C)
- Ancillary tests, as outlined in table 3, are recommended (Class IV, GCP)

In-hospital delay may account for 16% of total time lost between stroke onset and computed tomography (CT) [22]. Reasons for in-hospital delays are:

- a failure to identify stroke as an emergency
- inefficient in-hospital transport
- delayed medical assessment
- delay in imaging
- uncertainty in administering thrombolysis [20, 21, 24].

Stroke care pathways may allow care to be organized more effectively, although a meta-analysis [87] did not support their routine implementation. Such pathways may reduce delays in door-to-medical department time.

Table 3. Emergency diagnostic tests in acute stroke patients

In all patients	
1	Brain imaging: CT or MRI
2	ECG
3	Laboratory tests
	– Complete blood count and platelet count, prothrombin time or INR, partial thromboplastin time
	– Serum electrolytes, blood glucose
	– C-reactive protein or sedimentation rate
	– Hepatic and renal chemical analysis
When indicated	
4	Extracranial and transcranial Duplex/Doppler ultrasound
5	MRA or CTA
6	Diffusion and perfusion MR or perfusion CT
7	Echocardiography (transthoracic and/or transoesophageal)
8	Chest X-ray
9	Pulse oximetry and arterial blood gas analysis
10	Lumbar puncture
11	EEG
12	Toxicology screen

door-to-imaging time [88, 89], door-to-needle time [89] and, where appropriate, door-to-arteriography time.

Acute stroke care has to integrate EMS, ED staff and stroke care specialists. Communication and collaboration between EMS, ED staff, radiologists, clinical laboratories and neurologists are important for rapid delivery of treatment [90–92]. Integrating EMS and ED staff was found to increase the use of thrombolysis [93]. Hospitals where patients are not delivered directly to a stroke unit should implement a system allowing the ED to pre-notify the acute stroke team as soon as possible. Routinely informing ED physicians or stroke physicians during transport has been shown to be associated with reduced in-hospital delay [82, 94–96], increased use of thrombolysis [93, 94], decreased length of hospital stay [96] and decreased in-hospital mortality [93].

A stroke recognition instrument with high diagnostic accuracy is necessary for rapid triage [97]; stroke mimics like migraine and seizure might be a problem [98, 99]. Stroke recognition instruments such as Face-Arm-Speech Test and Recognition of Stroke in the Emergency Room (ROSIER) can assist the correct recognition of stroke by ED personnel [60, 98, 100].

A neurologist or stroke physician should be involved in the acute care of stroke patients and available in the ED [99]. Comparing neurologist care to non-neurologist care, two studies in the USA found that neurologists perform more extensive and costly testing, but that their patients had lower in-hospital and 90-day mortality rates and were less dependent on discharge [101, 102]. However, this might not be true for other countries like the UK, where most stroke physicians are not neurologists, but are still highly skilled in management of patients with TIA and stroke.

Reorganisation of stroke wards can help to avoid bottlenecks and unnecessary in-hospital transport. Brain imaging facilities should be relocated in or next to the stroke unit or the ED, and stroke patients should have priority access [90]. Neuroradiologists should be notified as early as possible [90]. In a Finnish study, in-hospital delays were decreased considerably by moving the CT scanner close to the ED and by implementing a pre-notifying system [95]. Thrombolysis should be started in the CT room or in the vicinity of the scanner. Finally, an arteriography suite should be readily accessible if endovascular treatment is required.

Written care protocols for acute stroke patients should be available; centres using such protocols were found to have higher thrombolysis rates [93]. Implementing a continuous quality improvement scheme can also diminish in-hospital delays [81, 103]. Benchmarks should be defined and measured for individual institutions, and have recently been developed for regional networks and countries. As a minimum requirement, door-to-imaging and door-to-treatment times should be monitored.

While only a minority of stroke patients present in an immediately life-threatening condition, many have significant physiological abnormalities or comorbidities. Symptoms and signs which may predict later complications such as space-occupying infarction, bleeding, or recurrent stroke, and medical conditions such as hypertensive crisis, co-existing MI, aspiration pneumonia, or cardiac and renal failure, must be recognized early. Stroke severity should be assessed by trained staff using the National Institutes of Health Stroke Scale (NIHSS) [104].

Initial examination should include:

- observation of breathing and pulmonary function
- early signs of dysphagia, preferably with a validated assessment form [105]
- evaluation of concomitant heart disease
- assessment of blood pressure (BP) and heart rate
- determination of arterial oxygen saturation using infrared pulse oximetry if available.

Simultaneously, blood samples for clinical chemistry, glucose, coagulation and haematology studies should be drawn, and a venous line inserted. The examination should be supplemented by a medical history that includes risk factors for stroke and cardiac disease, medications, conditions that may predispose to bleeding complications,

and markers for stroke mimics. A history of drug abuse, oral contraceptive use, infection, trauma or migraine may give important clues, particularly in young patients.

Stroke Services and Stroke Units

Recommendations

- It is recommended that all stroke patients should be treated in a stroke unit (Class I, Level A).
- It is recommended that healthcare systems ensure that acute stroke patients have access to high-technology medical and surgical stroke care when required (Class III, Level B).
- The development of clinical networks, including telemedicine, is recommended to expand access to high-technology specialist stroke care (Class II, Level B).

Providing Stroke Services

All acute stroke patients require specialist multidisciplinary care delivered in a stroke unit, and selected patients will require additional high-technology interventions. Health services need to establish the infrastructure to deliver these interventions to all patients who require them: the only reason for excluding patients from stroke units is if their condition does not warrant active management. Recent consensus documents [11, 106] have defined the roles of primary and comprehensive stroke centres (table 4).

Primary stroke centres are defined as centres with the necessary staffing, infrastructure, expertise and programmes to provide appropriate diagnosis and treatment for most stroke patients. Some patients with rare disorders, complex stroke, or multi-organ disease may need more specialized care and resources that are not available in primary stroke centres.

Comprehensive stroke centres are defined as centres that provide both appropriate diagnosis and treatment for most stroke patients, and also high-technology medical and surgical care (new diagnostic and rehabilitation methods, specialized tests, automatic monitoring of multiple physiological parameters, interventional radiology, vascular surgery, neurosurgery).

The organisation of clinical networks using telemedicine is recommended to facilitate treatment options not previously available at remote hospitals. Administration of rtPA during telemedicine consultations is feasible and safe [107]. Clinical networks using telemedicine systems achieve increased use of rtPA [80, 108] and better stroke care and clinical outcomes [80].

Table 4. Recommended requirements for centres managing acute stroke patients

Primary stroke centre	Comprehensive stroke centre
Availability of 24-hour CT scanning	MRI/MRA/CTA
Established stroke treatment guidelines and operational procedures, including intravenous rtPA protocols 24/7	Transoesophageal echocardiography
Close co-operation of neurologists, internists and rehabilitation experts	Cerebral angiography
Specially trained nursing personnel	Transcranial Doppler sonography
Early multidisciplinary stroke unit rehabilitation including speech therapy, occupational therapy and physical therapy	Extracranial and intracranial colour-coded duplex sonography
Neurosonological investigations within 24 h (extracranial Doppler sonography)	Specialized neuroradiological, neurosurgical and vascular surgical consultation (including telemedicine networks)
Transthoracic echocardiography	Carotid surgery
Laboratory examinations (including coagulation parameters)	Angioplasty and stenting
Monitoring of blood pressure, ECG, oxygen saturation, blood glucose, body temperature	Automated monitoring of pulse oximetry, blood pressure
Automated ECG monitoring at bedside	Established network of rehabilitation facilities to provide a continuous process of care, including collaboration with outside rehabilitation centre

Stroke Unit Care

An updated systematic review has confirmed significant reductions in death (3% absolute reduction), dependency (5% increase in independent survivors) and the need for institutional care (2% reduction) for patients treated in a stroke unit, compared with those treated in general wards. All types of patients, irrespective of gender, age, stroke subtype and stroke severity, appear to benefit from treatment in stroke units [61, 109]. These results have been confirmed in large observational studies of routine practice [110–112]. Although stroke unit care is more costly than treatment on general neurologi-

cal or medical wards, it reduces post-acute inpatient care costs [113, 114] and is cost-effective [115–118].

A stroke unit consists of a discrete area of a hospital ward that exclusively or nearly exclusively takes care of stroke patients and is staffed by a specialist multidisciplinary team [61]. The core disciplines of the team are medicine, nursing, physiotherapy, occupational therapy (OT), speech and language therapy (SLT) and social work [119]. The multidisciplinary team should work in a coordinated way through regular meetings to plan patient care. Programmes of regular staff education and training should be provided [119]. The typical components of stroke unit care in stroke unit trials [119] were:

- medical assessment and diagnosis, including imaging (CT, magnetic resonance imaging, MRI), and early assessment of nursing and therapy needs
- early management, consisting of early mobilization, prevention of complications, and treatment of hypoxia, hyperglycaemia, pyrexia and dehydration
- ongoing rehabilitation, involving coordinated multidisciplinary team care, and early assessment of needs after discharge.

Both acute and comprehensive stroke units admit patients acutely and continue treatment for several days. Rehabilitation stroke units admit patients after 1–2 weeks and continue treatment and rehabilitation for several weeks if necessary. Most of the evidence for effectiveness comes from trials of comprehensive stroke units and rehabilitation stroke units [61, 120]. Mobile stroke teams, which offer stroke care and treatment in a number of wards, probably do not influence important outcomes and cannot be recommended [121]. Such teams have usually been established in hospitals where stroke units were not available.

The stroke unit should be of sufficient size to provide specialist multidisciplinary care for the whole duration of hospital admission. Smaller hospitals may achieve this with a single comprehensive unit, but larger hospitals may require a pathway of care incorporating separate acute and rehabilitation units.

Diagnostics

Diagnostic Imaging

Recommendations

- In patients with suspected TIA or stroke, urgent cranial CT (Class I), or alternatively MRI (Class II), is recommended (Level A)
- If MRI is used, the inclusion of diffusion-weighted imaging (DWI) and T_2^*-weighted gradient echo sequences is recommended (Class II, Level A)
- In patients with TIA, minor stroke or early spontaneous recovery, immediate diagnostic work-up, including urgent vascular imaging (ultrasound, CT angiography, or MR angiography), is recommended (Class I, Level A)

Imaging of the brain and supplying vessels is crucial in the assessment of patients with stroke and TIA. Brain imaging distinguishes ischaemic stroke from intracranial haemorrhage and stroke mimics, and identifies the type and often also the cause of stroke; it may also help to differentiate irreversibly damaged tissue from areas that may recover, thus guiding emergency and subsequent treatment, and may help to predict outcome. Vascular imaging may identify the site and cause of arterial obstruction, and identifies patients at high risk of stroke recurrence.

General Principles

Stroke victims should have clear priority over other patients for brain imaging, because time is crucial. In patients with suspected TIA or stroke, general and neurological examination followed by diagnostic brain imaging must be performed immediately on arrival at the hospital so that treatment can be started promptly. Investigation of TIA is equally urgent because up to 10% of these patients will suffer stroke within the next 48 h. Immediate access to imaging is facilitated by pre-hospital notification and good communication with the imaging facility: stroke services should work closely with the imaging department to plan the best use of resources.

Diagnostic imaging must be sensitive and specific in detecting stroke pathology, particularly in the early phase of stroke. It should provide reliable images, and should be technically feasible in acute stroke patients. Rapid, focused neurological assessment is helpful to determine which imaging technique should be used. Imaging tests should take into account the patient's condition [122]; for example, up to 45% of patients with severe stroke may not tolerate MR examination because of their medical condition and contraindications [123–125].

Imaging in Patients with Acute Stroke

Patients admitted within 3 h of stroke onset may be candidates for intravenous thrombolysis [126]; CT is usually sufficient to guide routine thrombolysis. Patients arriving later may be candidates for trials testing extended time windows for thrombolysis or other experimental reperfusion strategies.

Plain CT is widely available, reliably identifies most stroke mimics, and distinguishes acute ischaemic from haemorrhagic stroke within the first 5–7 days [127–129]. Immediate CT scanning is the most cost-effective strategy for imaging acute stroke patients [130], but is not sensitive for old haemorrhage. Overall, CT is less sensitive than MRI, but equally specific, for early ischaemic changes [131]. Two thirds of patients with moderate to severe stroke have visible ischaemic changes within the first few hours [131–135], but no more than 50% of patients with minor stroke have a visible relevant ischaemic lesion on CT, especially within the first few hours of stroke [136]. Training in identification of early ischaemic changes on CT [135, 137, 138], and the use of scoring systems [134], improve detection of early ischaemic changes.

Early CT changes in ischaemic stroke include decreases in tissue X-ray attenuation, tissue swelling with effacement of cerebrospinal fluid spaces, and arterial hyperattenuation, which indicates the presence of intrahuminal thrombus with high specificity [139]. CT is highly specific for the early identification of ischaemic brain damage [132, 140, 141]. The presence of early signs of ischaemia on CT should not exclude patients from thrombolysis within the first 3 h, though patients with a hypoattenuating ischaemic lesion which exceeds one third of the middle cerebral artery (MCA) territory may benefit less from thrombolysis [126, 134, 135, 142, 143].

Some centres prefer to use MRI as first-line routine investigation for acute stroke. MRI with DWI has the advantage of higher sensitivity for early ischaemic changes than CT [131]. This higher sensitivity is particularly useful in the diagnosis of posterior circulation stroke and lacunar or small cortical infarctions. MRI can also detect small and old haemorrhages for a prolonged period with T_2* (gradient echo) sequences [144]. However, DWI can be negative in patients with definite stroke [145].

Restricted diffusion on DWI, measured by the apparent diffusion coefficient (ADC), is not 100% specific for ischaemic brain damage. Although abnormal tissue on DWI often proceeds to infarction it can recover, which indicates that DWI does not show only permanently damaged tissue [146, 147]. Tissue with only modestly reduced ADC values may be permanently damaged; there is as yet no reliable ADC threshold to differentiate dead from still viable tissue [148, 149]. Other MRI sequences (T_2, FLAIR, T_1) are less sensitive in the early detection of ischaemic brain damage.

MRI is particularly important in acute stroke patients with unusual presentations, stroke varieties, and uncommon aetiologies, or in whom a stroke mimic is suspected but not clarified on CT. If arterial dissection is suspected, MRI of the neck with fat-suppressed T_1-weighted sequences is required to detect intramural haematoma.

MRI is less suited for agitated patients or for those who may vomit and aspirate. If necessary, emergency life support should be continued while the patient is being imaged, as patients (especially those with severe stroke) may become hypoxic while supine during imaging [125]. The risk of aspiration is increased in the substantial proportion of patients who are unable to protect their airway.

Perfusion imaging with CT or MRI and angiography may be used in selected patients with ischaemic stroke (e.g. unclear time window, late admission) to aid the decision on whether to use thrombolysis, although there is no clear evidence that patients with particular perfusion patterns are more or less likely to benefit from thrombolysis [150–153]. Selected patients with intracranial arterial occlusion may be candidates for intra-arterial thrombolysis, although there is only limited evidence to support this [154, 155]. Patients with combined obstructions of the internal carotid artery (ICA) and MCA have less chance of recovering with intravenous thrombolysis than patients with isolated MCA obstructions [156]. In patients with MCA trunk occlusions, the frequency of severe extracranial occlusive disease in the carotid distribution is high [157, 158].

Mismatch between the volume of brain tissue with critical hypoperfusion (which can recover after reperfusion) and the volume of infarcted tissue (which does not recover even with reperfusion) can be detected with MR diffusion/perfusion imaging with moderate reliability [159], but this is not yet a proven strategy for improving the response to thrombolysis up to 9 h [160]. There is disagreement on how to best identify irreversible ischaemic brain injury and to define critically impaired blood flow [150, 153, 161]. Quantification of MR perfusion is problematic [162], and there are widely differing associations between perfusion parameters and clinical and radiological outcomes [150]. Decreases in cerebral blood flow on CT are associated with subsequent tissue damage [151, 152], but the therapeutic value of CT perfusion imaging is not yet established. Although infarct expansion may occur in a high proportion of patients with mismatch, up to 50% of patients without mismatch may also have infarct growth and so might benefit from tissue salvage [153, 163]. The 'imaging/clinical' mismatch, i.e. the mismatch between the extent of the lesion seen on DWI or CT and the extent of the lesion as expected from the severity of the neurological deficit, has produced mixed re-

sults [164, 165]. Hence, neither perfusion imaging with CT or MRI nor the mismatch concept can be recommended for routine treatment decisions.

Microhaemorrhages are present on T_2* MRI in up to 60% of patients with haemorrhagic stroke, and are associated with older age, hypertension, diabetes, leukoaraiosis, lacunar stroke, and amyloid angiopathy [166]. The incidence of symptomatic intracranial haemorrhage following thrombolysis in ischaemic stroke patients was not increased in those having cerebral microbleeds on pretreatment T_2*-weighted MRI [167].

Vascular imaging should be performed rapidly to identify patients with tight symptomatic arterial stenosis who could benefit from endarterectomy or angioplasty. Non-invasive imaging with colour-coded duplex imaging of the extracranial and intracranial arteries, CT angiography (CTA), or contrast-enhanced MR angiography (CE-MRA) is widely available. These approaches are relatively risk-free, whereas intra-arterial angiography has a 1–3% risk of causing stroke in patients with symptomatic carotid lesions [168, 169]. Digital subtraction angiography may be needed in some circumstances, for example when other tests have been inconclusive.

Carotid ultrasound, MRA and CTA visualise carotid stenosis. Systematic reviews and individual patient data meta-analysis indicate that CE-MRA is the most sensitive and specific non-invasive imaging modality for carotid artery stenosis, closely followed by Doppler ultrasound and CTA, with non-contrast MRA being the least reliable [170, 171].

Some data suggest that vertebrobasilar TIA and minor stroke are associated with a high risk of recurrent stroke [172]. Extracranial vertebral ultrasound diagnosis is useful, but intracranial ultrasound of the vertebrobasilar system can be misleading due to low specificity. Limited data suggest that contrast-enhanced MRA and CTA offer better non-invasive imaging of the intracranial vertebral and basilar arteries [173].

Unlike other imaging modalities ultrasound is fast, non-invasive and can be administered using portable machines. It is therefore applicable to patients unable to co-operate with MRA or CTA [158]. However, Doppler studies alone often provide only limited information, are investigator dependent and require skilled operators, although they allow repeated measurements at the bedside.

Transcranial Doppler ultrasound (TCD) is useful for the diagnosis of abnormalities in the large cerebral arteries at the base of the skull. However, between 7 and 20% of acute stroke patients, particularly elderly individuals and those from certain ethnic groups do not have an adequate acoustic window [174, 175]. This problem can be considerably reduced by using ultrasound contrast agents, which also allow perfusion studies in the acute phase [176–178] and continuous monitoring of cerebral haemodynamic responses [179]. The combination of ultrasound imaging techniques and MRA reveals excellent results equal to digital subtraction angiography [180]. Cerebral reactivity and cerebral autoregulation are impaired in patients with occlusive extracerebral arterial disease (particularly carotid stenosis and occlusion) and inadequate collateral supply, who are at increased risk of recurrent stroke [181, 182]. TCD is the only technique that detects circulating intracranial emboli [183], which are particularly common in patients with large artery disease. In patients with symptomatic carotid artery stenoses, they are a strong independent predictor of early recurrent stroke and TIA [184], and have been used as a surrogate marker to evaluate antiplatelet agents [185]. TCD microbubble detection can be used to identify a right-to-left shunt which mainly results from a patent foramen ovale (PFO) [186].

Imaging in Patients with TIA, Minor Non-Disabling Stroke, and Stroke with Spontaneous Recovery

Patients presenting with TIA are at high risk of early recurrent stroke (up to 10% in the first 48 h) [187]. They therefore need urgent clinical diagnosis to treat associated general abnormalities, modify active risk factors and identify specific treatable causes, particularly arterial stenosis and other embolic sources. Vascular imaging is a priority in those patients with TIA or minor stroke, more than in those with major stroke in whom surgery is not going to be of benefit in the short term. Immediate preventive treatment will reduce stroke, disability and death [86, 188]. Simple clinical scoring systems can be used to identify patients at particularly high risk [187]. Patients with minor non-disabling stroke and rapid spontaneous clinical recovery are also at high risk of recurrent stroke [58].

Patients with widely varying brain pathology may present with transient neurological deficits indistinguishable from TIA. CT reliably detects some of these pathologies (e.g. intracerebral haemorrhage, subdural haematoma, tumours) [130], but others (e.g. multiple sclerosis, encephalitis, hypoxic brain damage, etc.) are better identified on MRI, while others (e.g. acute metabolic disturbances) are not visible at all. Intracranial haemorrhage is a rare cause of TIA.

Between 20–50% of patients with TIAs may have acute ischaemic lesions on DWI [145, 189, 190]. These patients are at increased risk of early recurrent disabling stroke [190]. However, there is currently no evidence that DWI provides better stroke prediction than clinical risk scores [191]. The risk of recurrent disabling stroke is also increased in patients with TIA and an infarct on CT [192].

The ability of DWI to identify very small ischaemic lesions may be particularly helpful in patients presenting late or in patients with mild non-disabling stroke, in whom the diagnosis may be difficult to establish on clinical grounds [131]. T_2* MRI is the only reliable method to identify haemorrhages after the acute phase, when blood is no longer visible on CT [144].

Other Diagnostic Tests

Recommendations

- In patients with acute stroke and TIA, early clinical evaluation, including physiological parameters and routine blood tests, is recommended (Class I, Level A)
- For all stroke and TIA patients, a sequence of blood tests is recommended (tables 3 and 5)
- It is recommended that all acute stroke and TIA patients should have a 12-lead electrocardiography (ECG). In addition, continuous ECG recording is recommended for ischaemic stroke and TIA patients (Class I, Level A)
- It is recommended that for stroke and TIA patients seen after the acute phase, 24-hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of stroke are found (Class I, Level A)
- Echocardiography is recommended in selected patients (Class III, Level B)

Cardiac Evaluation

Cardiac and ECG abnormalities are common in acute stroke patients [193]. In particular, prolonged heart rate corrected QT interval, ST depression, and T wave inversion are prevalent in acute ischaemic stroke, especially if the insular cortex is involved [194, 195]. Hence, all acute stroke and TIA patients should have a 12-channel ECG.

Cardiac monitoring should be conducted routinely after an acute cerebrovascular event to screen for serious cardiac arrhythmias. It is unclear whether continuous ECG recording at the bedside is equivalent to Holter monitoring for the detection of atrial fibrillation (AF) in acute stroke patients. Holter monitoring is superior to routine ECG for the detection of AF in patients anticipated to have thromboembolic stroke with sinus rhythm [196]; however, serial 12-channel ECG might be sufficient to detect new AF in a stroke unit setting [197]. A recent systematic review found that new AF was detected by Holter ECG in 4.6% of patients with recent ischaemic stroke or TIA, irrespective of baseline ECG and clinical examination [198]. Extended duration of monitoring, prolonged event loop recording, and confining Holter monitoring to patients with non-lacunar stroke may improve detection rates [199].

Table 5. Subsequent laboratory tests, according to the type of stroke and suspected aetiology

All patients	Full blood count, electrolytes, glucose, lipids, creatinine, CRP or erythrocyte sedimentation rate
Cerebral venous thrombosis, hypercoagulopathy	Thrombophilia screen, AT3, factor 2, 5. mutations, factor 8, protein C, protein S, antiphospholipid antibodies, d-dimer, homocysteine
Bleeding disorder	INR, activated partial thromboplastin time, fibrinogen, etc.
Vasculitis or systemic disorder	Cerebral spinal fluid, autoantibody screen, specific antibodies or PCR for HIV, syphilis, borteliosis, tuberculosis, fungi, illicit drug screening, blood culture
Suspected genetic disorders, e.g. mitochondrial disorders (MELAS), CADASIL, sickle cell disease, Fabry disease, multiple cavernoma, etc.	Genetic testing

Echocardiography can detect many potential causes of stroke [200], but there is controversy about the indications for, and type of, echocardiography in stroke and TIA patients. Transoesophageal echocardiography (TOE) has been claimed to be superior to transthoracic echocardiography for the detection of potential cardiac sources of embolism [201], independent of age [202].

Echocardiography is particularly required in patients with:

- evidence of cardiac disease on history, examination, or ECG
- suspected cardiac source of embolism (e.g. infarctions in multiple cerebral or systemic arterial territories)
- suspected aortic disease
- suspected paradoxical embolism
- no other identifiable causes of stroke.

Table 6. NNT to prevent one stroke per year in patients who undergo surgery for ICA stenosis (modified from Hankey and Warlow [583] and Rothwell et al. [339])

Disease	NNT to avoid one stroke/year
Asymptomatic (60–99%)	85
Symptomatic (70–99%)	27
Symptomatic (50–69%)	75
Symptomatic (>50%) in men	45
Symptomatic (>50%) in women	180
Symptomatic (>50%) >75 years	25
Symptomatic (>50%) <65 years	90
Symptomatic (>50%) <2 weeks after the event	25
Symptomatic (>50%) >12 weeks after the event	625
Symptomatic (≤50%)	No benefit

All percentages reflect the NASCET method.

Transthoracic echocardiography is sufficient for evaluation of mural thrombi, particularly in the apex of the left ventricle; this technique has >90% sensitivity and specificity for ventricular thrombi after MI [203]. TOE is superior for evaluation of the aortic arch, left atrium, and atrial septum [200]. It also allows risk stratification for further thromboembolic events in patients with AF [204].

The role of cardiac CT and cardiac MRI in the detection of embolic sources in stroke patients has not been evaluated systematically.

Blood Tests

Blood tests required on emergency admission are listed in table 3. Subsequent tests depend on the type of stroke and suspected aetiology (table 5).

Primary Prevention

The aim of primary prevention is to reduce the risk of stroke in asymptomatic people. Relative risk (RR), absolute risk (AR), odds ratio (OR), numbers needed to treat (NNT) to avoid one major vascular event per year, and numbers needed to harm to cause one major complication per year, are provided for each intervention in tables 6–8.

Management of Vascular Risk Factors

Recommendations

- BP should be checked regularly. It is recommended that high BP should be managed with lifestyle modification and individualized pharmacological therapy (Class I, Level A) aiming at normal levels of 120/80 mm Hg (Class IV, GCP). For prehypertensive (120–139/80–90 mm Hg) with congestive heart failure, MI, diabetes, or chronic renal failure antihypertensive medication is indicated (Class I, Level A)
- Blood glucose should be checked regularly. It is recommended that diabetes should be managed with lifestyle modification and individualized pharmacological therapy (Class IV, Level C). In diabetic patients, high BP should be managed intensively (Class I, Level A) aiming for levels below 130/80 mm Hg (Class IV, Level C). Where possible, treatment should include an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (Class I, Level A)
- Blood cholesterol should be checked regularly. It is recommended that high blood cholesterol (e.g. LDL >150 mg/dl; 3.9 mM) should be managed with lifestyle modification (Class IV, Level C) and a statin (Class I, Level A)
- It is recommended that cigarette smoking be discouraged (Class III, Level B)
- It is recommended that heavy use of alcohol be discouraged (Class III, Level B)
- Regular physical activity is recommended (Class III, Level B)
- A diet low in salt and saturated fat, high in fruit and vegetables and rich in fibre is recommended (Class III, Level B)
- Subjects with an elevated body mass index are recommended to take a weight-reducing diet (Class III, Level B)
- Antioxidant vitamin supplements are not recommended (Class I, Level A)
- Hormone replacement therapy is not recommended for the primary prevention of stroke (Class I, Level A)

A healthy lifestyle, consisting of abstinence from smoking, low-normal body mass index, moderate alcohol consumption, regular exercise and healthy diet, is associated with a reduction in ischaemic stroke (RR 0.29, 95% CI 0.14–0.63) [205].

High Blood Pressure

A high (>120/80 mm Hg) BP is strongly and directly related to vascular and overall mortality without evidence of any threshold [206]. Lowering BP substantially reduces stroke and coronary risks, depending on the magnitude of the reduction [207–209]. BP should be lowered to 140/85 mm Hg or below [210]; antihypertensive treatment should be more aggressive in diabetic patients (see below) [211]. A combination of two or more antihypertensive agents is often necessary to achieve these targets.

Most studies comparing different drugs do not suggest that any class is superior [207, 208, 212]. However, the LIFE (Losartan Intervention for Endpoint reduction in

Table 7. RR reduction (RRR), AR reduction (ARR) and NNT to avoid one major vascular event per year in patients with antithrombotic therapy (modified from CAPRIE Steering Committee [319], Halkes et al. [322], Hankey and Warlow [583])

Disease	Treatment	RRR %	ARR %/year	NNT to avoid 1 event/year
Non-cardioembolic ischaemic stroke or TIA	Aspirin/PCB	13	1.0	100
	Aspirin + DIP/PCB	28	1.9	53
	Aspirin + DIP/aspirin	18	1.0	104
	Clop/PCB	23	1.6	62
	Clop/aspirin	10	0.6	166
Atrial fibrillation (primary prevention)	Warfarin/PCB	62	2.7	37
	Aspirin/PCB	22	1.5	67
Atrial fibrillation (secondary prevention)	Warfarin/PCB	67	8	13
	Aspirin/PCB	21	2.5	40

PCB = Placebo; Clop = clopidogrel; DIP = dipyridamole.

Table 8. RRR, ARR and NNT to avoid one major vascular event per year in patients with risk factor modifications (modified from Yusuf et al. [288], PROGRESS Collaborative Group [290], Amarenco et al. [294], Hankey and Warlow [583])

Clinical condition	Treatment	RRR %	ARR %/year	NNT to avoid 1 event/year
General population with increased BP	Antihypertensive	42	0.4	250
General population with increased vascular risk	ACE inhibitor	22	0.65	154
Post-stroke/TIA with increased BP	Antihypertensive	31	2.2	45
Post-stroke/TIA with normal BP	ACE inhibitor ± diuretic	24	0.85	118
Post-stroke/TIA	Statins	16	0.44	230
	Smoking cessation	33	2.3	43

hypertension) trial found that losartan was superior to atenolol in hypertensive patients with left ventricular hypertrophy (NNT to prevent stroke 270) [213, 214]. Similarly, the ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack) trial found that chlorthalidone was more effective than amlodipine and lisinopril [215]. Beta-blockers may still be considered an option for initial and subsequent antihypertensive treatment [210]. In elderly subjects, controlling isolated systolic hypertension (systolic BP >140 mm Hg and diastolic BP <90 mm Hg) is beneficial [208, 216].

Diabetes Mellitus

There is no evidence that improving glucose control reduces stroke [217]. In diabetic patients, BP should be lowered to below 130/80 mm Hg [211]. Treatment with a statin reduces the risk of major cardiovascular (CV) events, including stroke [218–220].

Hyperlipidaemia

In a review of 26 statin trials (95,000 patients), the incidence of stroke was reduced from 3.4 to 2.7% [221]. This was due mainly to a reduction in non-fatal stroke, from 2.7 to 2.1%. The review included the Heart Protection Study which was, in part, a secondary prevention trial [222]; this trial found an excess of myopathy of one per 10,000 patients treated per annum [222]. There are no data to suggest that statins prevent stroke in patients with low-density lipoprotein cholesterol below 150 mg/dl (3.9 mM).

Cigarette Smoking

Observational studies have shown cigarette smoking to be an independent risk factor for ischaemic stroke [223] in both men and women [224–228]. Spousal cigarette smoking may be associated with an increased stroke risk [229]. A meta-analysis of 22 studies indicates that

smoking doubles the risk of ischaemic stroke [230]. Subjects who stop smoking reduce this risk by 50% [225]. Making workplaces smoke-free would result in considerable health and economic benefits [231].

Alcohol Consumption

Heavy alcohol drinking (>60 g/day) increases the risk of ischaemic stroke (RR 1.69; 95% CI 1.34–2.15) and haemorrhagic stroke (RR 2.18; 95% CI 1.48–3.20). In contrast, light consumption (<12 g/day) is associated with a reduction in all stroke (RR 0.83; 95% CI 0.75–0.91) and ischaemic stroke (RR 0.80; 95% CI 0.67–0.96), and moderate consumption (12–24 g/day) with a reduction in ischaemic stroke (RR 0.72; 95% CI 0.37–0.91) [232]. Red wine consumption is associated with the lowest risk in comparison with other beverages [233]. BP elevation appears to be an important intermediary in the relation between alcohol consumption and stroke [234].

Physical Activity

In a meta-analysis of cohort and case-control studies, physically active individuals had a lower risk of stroke or death than those with low activity (RR 0.73; 95% CI 0.67–0.79). Similarly, moderately active individuals had a lower risk of stroke, compared with those who were inactive (RR 0.80; 95% CI 0.74–0.86) [235]. This association is mediated, in part, through beneficial effects on body weight, BP, serum cholesterol, and glucose tolerance. Leisure-based physical activity (2–5 h per week) has been independently associated with a reduced severity of ischaemic stroke at admission and better short-term outcome [236].

Diet

Fruit, Vegetable, and Fish Intake

In observational studies, high fruit and vegetable intake was associated with a decreased risk of stroke, compared with lower intake (RR 0.96 for each increment of 2 servings/day; 95% CI 0.93–1.00) [237]. The risk of ischaemic stroke was lower in people who consumed fish at least once per month (RR 0.69; 95% CI 0.48–0.99) [238]. Whole grain intake was associated with a reduction in CV disease (OR 0.79; 95% CI 0.73–0.85) but not stroke [239]. Dietary calcium intake from dairy products was associated with lower mortality from stroke in a Japanese population [240]. However, in a further study there was no interaction between the intake of total fat or cholesterol, and stroke risk in men [241].

In a randomized controlled trial in women, dietary interventions did not reduce the incidence of coronary events and stroke despite there being an 8.2% reduction of total fat intake and an increased consumption of vegetables, fruits and grains [242].

Body Weight

A high body mass index (≥25) is associated with an increased risk of stroke in men [243] and women [244], mainly mediated by concomitant arterial hypertension and diabetes. Abdominal adiposity is a risk factor for stroke in men but not women [245]. Although weight loss reduces BP [246], it does not lower stroke risk [247].

Vitamins

A low intake of vitamin D is associated with an increased risk of stroke [248], but supplements of calcium plus vitamin D do not reduce the risk of stroke [249]. Supplements of tocopherol and beta carotene do not reduce stroke [250]. A meta-analysis of trials with vitamin E supplementation found that it might increase mortality when used at high doses (≥400 IU/day) [251].

High homocysteine levels are associated with increased stroke risk (OR 1.19; 95% CI 1.05–1.31) [252]. Since folic acid fortification of enriched grain products was mandated by the US Food and Drug Administration, there has been a reduction in stroke mortality rates, in contrast to countries without fortification [253]. A meta-analysis concluded that folic acid supplementation can reduce the risk of stroke (RR 0.82; 95% CI 0.68–1.00) [254]; the benefit was greatest in trials with long treatment durations or larger homocysteine-lowering effects, and in countries where grain was not fortified.

Postmenopausal Oestrogen Replacement Therapy

Stroke rates rise rapidly in women after the menopause. However, in an analysis based on a 16-year follow-up of 59,337 postmenopausal women participating in the Nurses' Health Study, there was only a weak association between stroke and oestrogen replacement [255]. According to the HERS II trial, hormone replacement in healthy women is associated with an increased risk of ischaemic stroke [256]. A Cochrane systematic review [257] found hormone replacement therapy to be associated with an increased risk of stroke (RR 1.44; 95% CI 1.10–1.89). A secondary analysis of the Women's Health Initiative randomized controlled trial suggests that the risk of stroke is increased with hormone replacement therapy only in women with prolonged hormone use (>5 years; RR 1.32; 95% CI 1.12–1.56) [258, 259].

Antithrombotic Therapy

Recommendations

- Low-dose aspirin is recommended in women aged 45 years or more who are not at increased risk for intracerebral haemorrhage and who have good gastrointestinal tolerance, however, its effect is very small (Class I, Level A)
- It is recommended that low-dose aspirin may be considered in men for the primary prevention of MI; however, it does not reduce the risk of ischaemic stroke (Class I, Level A)
- Antiplatelet agents other than aspirin are not recommended for primary stroke prevention (Class IV, GCP)
- Aspirin may be recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors (Class I, Level A)
- Unless contraindicated, either aspirin or an oral anticoagulant (international normalized ratio, INR, 2.0–3.0) is recommended for patients with non-valvular AF who are aged 65–75 years and free of vascular risk factors (Class I, Level A)
- Unless contraindicated, an oral anticoagulant (INR 2.0–3.0) is recommended for patients with non-valvular AF who are aged >75, or who are younger but have risk factors such as high BP, left ventricular dysfunction, or diabetes mellitus (Class I, Level A)
- It is recommended that patients with AF who are unable to receive oral anticoagulants should be offered aspirin (Class I, Level A)
- It is recommended that patients with AF who have mechanical prosthetic heart valves should receive long-term anticoagulation with a target INR based on the prosthesis type, but not less than INR 2–3 (Class II, Level B)
- Low-dose aspirin is recommended for patients with asymptomatic ICA stenosis >50% to reduce their risk of vascular events (Class II, Level B)

Low-Risk Subjects

Six large randomized trials have evaluated the benefits of aspirin for the primary prevention of CV events in men and women (47,293 on aspirin, 45,580 controls) with a mean age of 64.4 years [260–265]. Aspirin reduced coronary events and CV events, but not stroke, CV mortality, or all-cause mortality [266]. In women, aspirin reduced stroke (OR 0.83; 95% CI 0.70–0.97) and ischaemic stroke (OR 0.76; 95% CI 0.63–0.93) [267]. In a separate study in 39,876 healthy women aged 45 years or more, aspirin reduced stroke (RR 0.83; 95% CI 0.69–0.99) and ischaemic stroke (RR 0.76; 95% CI 0.63–0.93), and caused a non-significant increase in haemorrhagic stroke, over 10 years; it did not reduce the risk of fatal or nonfatal MI, or CV death [268].

No data are currently available on the use of other antiplatelet agents in primary prevention in low-risk subjects.

Subjects with Vascular Risk Factors

A systematic review of randomized studies comparing antithrombotic agents with placebo in patients with elevated BP and no prior CV disease showed that aspirin did not reduce stroke or total CV events [267]. In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, the combination of aspirin and clopidogrel was less effective than aspirin alone in the subgroup of patients with multiple vascular risk factors but no ischaemic event [269].

Large Artery Atheroma

Patients with atherosclerotic arterial disease have an increased risk of MI, stroke, and CV death. Aspirin reduces MI in patients with asymptomatic carotid artery disease [270], and reduces stroke after carotid artery surgery [271].

Atrial Fibrillation

AF is a strong independent risk factor for stroke. A meta-analysis of randomized trials with at least 3 months' follow-up showed that antiplatelet agents reduced stroke (RR 0.78; 95% CI 0.65–0.94) in patients with non-valvular AF [272]. Warfarin (target INR 2.0–3.0) is more effective than aspirin at reducing stroke (RR 0.36; 95% CI 0.26–0.51) [272]. As the risk of stroke in people with AF varies considerably, risk stratification should be used to determine whether patients should be given oral anticoagulation, aspirin or nothing [14]. Oral anticoagulation is more effective in patients with AF who have one or more risk factors, such as previous systemic embolism, age over 75 years, high BP or poor left ventricular function [14]. In the meta-analysis described above, absolute increases in major extracranial haemorrhage were less than the absolute reductions in stroke [272]. The WASPO (Warfarin vs. Aspirin for Stroke Prevention in Octogenarians) [273] and BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) [274] trials showed that warfarin was safe and effective in older individuals. The ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) study found that the combination of aspirin and clopidogrel was less effective than warfarin and had a similar bleeding rate [275].

Patients with a prosthetic heart valve, with or without AF, should receive long-term anticoagulation with a target INR based on the prosthesis type (bio-prosthetic valves: INR 2.0–3.0; mechanical valves: INR 3.0–4.0 [276]).

Carotid Surgery and Angioplasty

Recommendations

- Carotid surgery is not recommended for asymptomatic individuals with significant carotid stenosis (North American Symptomatic Carotid Endarterectomy Trial—NASCET 60–99%), except in those at high risk of stroke (Class I, Level C)
- Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis (Class IV, GCP)
- It is recommended that patients should take aspirin before and after surgery (Class I, Level A)

Trials of carotid surgery for asymptomatic carotid stenosis have concluded that although surgery reduces the incidence of ipsilateral stroke (RR 0.47–0.54) and any stroke, the absolute benefit is small (approximately 1% per annum) [277–279], whereas the perioperative stroke or death rate is 3%. Medical management is the most appropriate option for most asymptomatic subjects; only centres with a perioperative complication rate of 3% or less should contemplate surgery. Patients with a high risk of stroke (men with stenosis of more than 80% and a life expectancy of more than 5 years) may derive some benefit from surgery in appropriate centres [277, 279]. All stenoses are graded following the NASCET method (distal stenosis) [280].

Carotid endarterectomy (CEA) is effective in younger patients, and possibly also in older individuals, but does not appear to benefit women [277]. Patients with occlusion of the ICA contralateral to the operated carotid artery do not benefit from CEA [281, 282]. The risk of ipsilateral stroke increases with the degree of stenosis [281, 283]; CEA appears to be effective irrespective of the degree of ipsilateral stenosis over the range of 60–99% [277]. CEA is not beneficial for asymptomatic patients who have a life expectancy of less than 5 years. Aspirin should not be stopped in patients undergoing carotid surgery [284]. Patients should be followed-up by the referring physician after surgery. There are no data from randomized trials about the benefits and risks of carotid angioplasty, compared with CEA, in asymptomatic patients [285].

Secondary Prevention

Optimal Management of Vascular Risk Factors

Recommendations

- It is recommended that BP be checked regularly. BP lowering is recommended after the acute phase, including in patients with normal BP (Class I, Level A)
- It is recommended that blood glucose should be checked regularly. It is recommended that diabetes should be managed with lifestyle modification and individualized pharmacological therapy (Class IV, GCP)
- In patients with type 2 diabetes who do not need insulin, treatment with pioglitazone is recommended after stroke (Class III, Level B)
- Statin therapy is recommended in subjects with non-cardioembolic stroke (Class I, Level A)
- It is recommended that cigarette smoking be discouraged (Class III, Level C)
- It is recommended that heavy use of alcohol be discouraged (Class IV, GCP)
- Regular physical activity is recommended (Class IV, GCP)
- A diet low in salt and saturated fat, high in fruit and vegetables, and rich in fibre is recommended (Class IV, GCP)
- Subjects with an elevated body mass index are recommended to adopt a weight-reducing diet (Class IV, Level C)
- Antioxidant vitamin supplements are not recommended (Class I, Level A)
- Hormone replacement therapy is not recommended for the secondary prevention of stroke (Class I, Level A)
- Sleep-disordered breathing such as obstructive sleep apnoea (OSA) is recommended to be treated with continuous positive airway pressure breathing (Class III, Level GCP)
- It is recommended that endovascular closure of PFO be considered in patients with cryptogenic stroke and high-risk PFO (Class IV, GCP)

High Blood Pressure

A meta-analysis of seven randomized controlled trials showed that antihypertensive drugs reduced stroke recurrence after stroke or TIA (RR 0.76; 95% CI 0.63–0.92) [286]. This analysis included the PATS (indapamide, a diuretic), HOPE (ramipril) and PROGRESS (perindopril, with or without indapamide) studies [287–290]. The reduction in stroke occurs regardless of BP and type of stroke [290]. Hence, BP should be lowered and monitored indefinitely after stroke or TIA. The absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of about 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg [291]. However, BP should not be lowered intensively in patients with suspected haemodynamic stroke or in those with bilateral carotid stenosis. The angiotensin receptor antagonist eprosartan may be more effective than the calcium channel blocker nitrendipine [292].

Diabetes Mellitus

The prospective, double-blind PROactive trial randomized 5,238 patients with type 2 diabetes and a history of macrovascular disease to pioglitazone or placebo. In patients with previous stroke (n = 486 in the piogli-

tazone group, n = 498 in the placebo group), there was a trend towards benefit with pioglitazone for the combined end point of death and major vascular events (HR 0.78; 95% CI 0.60–1.02; p = 0.067). In a secondary analysis, pioglitazone reduced fatal or nonfatal stroke (HR 0.53; 95% CI 0.34–0.85; p = 0.0085) and CV death, nonfatal MI, or nonfatal stroke (HR 0.72; 95% CI 0.52–1.00; p = 0.0467) [293].

Hyperlipidaemia

In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, statin therapy with atorvastatin reduced stroke recurrence (HR 0.84; 95% CI 0.71–0.99) [294], while in the Heart Protection Study simvastatin reduced vascular events in patients with prior stroke, and reduced stroke in patients with other vascular disease (RR 0.76) [222]. Neither trial assessed efficacy by stroke subtype, and SPARCL did not include patients with presumed cardioembolic stroke [222, 294]. The risk of haemorrhagic stroke was slightly increased in both trials [222, 294]. The AR reduction achieved with statin therapy is low (NNT 112–143 for 1 year). Statin withdrawal at the acute stage of stroke may be associated with an increased risk of death or dependency [295].

Cigarette Smoking

There are no specific data in secondary prevention. See 'Primary Prevention'.

Diet

Overweight

There are no specific data in secondary prevention. See 'Primary Prevention'. Weight loss may be beneficial after stroke as it lowers BP [246].

Vitamins

Beta carotene increased the risk of CV death in a meta-analysis of primary and secondary prevention trials (RR 1.10; 95% CI 1.03–1.17) [296]. Vitamin E supplementation does not prevent vascular events [297]. Fat-soluble antioxidant supplements may increase mortality [298].

Vitamins which lower homocysteine (folate, B_{12}, B_6) do not appear to reduce stroke recurrence and may increase vascular events [299–302], but further trials are ongoing [303].

Sleep-Disordered Breathing

Sleep-disordered breathing represents both a risk factor and a consequence of stroke and is linked with poorer long-term outcome and increased long-term stroke mortality [304]. More than 50% of stroke patients have sleep-disordered breathing, mostly in the form of OSA. This can improve spontaneously after stroke, but may need treatment. Continuous positive airway pressure is the treatment of choice for OSA. Oxygen and other forms of ventilation may be helpful in other (e.g. central) forms of SDB.

Patent Foramen Ovale

Case reports and case control studies indicate an association between the presence of PFO and cryptogenic stroke in both younger and older stroke patients [305, 306]. Two population-based studies pointed in the same direction but did not confirm a significant association [307, 308]. In patients with PFO alone the overall risk of recurrence is low. However, when the PFO is combined with an atrial septal aneurysm, an Eustachian valve, a Chiari network, or in patients who have suffered more than one stroke the risk of recurrence can be substantial [309]. Endovascular closure of PFOs with or without septal aneurysms is feasible in such patients [310] and may lower the risk of recurrent stroke compared to medical treatment [311]; however, RCTs are still lacking.

Postmenopausal Oestrogen Replacement Therapy

Hormone replacement therapy does not protect against vascular events and may increase stroke severity [312].

Antithrombotic Therapy

Recommendations

- It is recommended that patients receive antithrombotic therapy (Class I, Level A).
- It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A).
- The combination of aspirin and clopidogrel is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A).
- It is recommended that patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP).
- Oral anticoagulation (INR 2.0–3.0) is recommended after ischaemic stroke associated with AF (Class I, Level A). Oral anticoagulation is not recommended in patients with comorbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding (Class III, Level C). Increasing age alone is not a contraindication to oral anticoagulation (Class I, Level A).

- It is recommended that patients with cardioembolic stroke unrelated to AF should receive anticoagulants (INR 2.0–3.0) if the risk of recurrence is high (Class III, Level C)
- It is recommended that anticoagulation should not be used after non-cardio-embolic ischaemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery, cervical artery dissection, or PFO in the presence of proven deep vein thrombosis (DVT) or atrial septal aneurysm (Class IV, GCP)
- It is recommended that combined low-dose aspirin and dipyridamole should be given if oral anticoagulation is contraindicated (Class IV, GCP)

Antiplatelet Therapy

Antiplatelet therapy reduces vascular events, including non-fatal MI, nonfatal stroke and vascular death in patients with previous stroke or TIA (RR 0.78; 95% CI 0.76–0.80) [313].

Aspirin

Aspirin reduces recurrence irrespective of dose (50–1,300 mg/day) [314–317], although high doses (>150 mg/day) increase adverse events. In patients with symptomatic intracranial atherosclerosis, aspirin is as effective as oral anticoagulation and has fewer complications [318].

Clopidogrel

Clopidogrel is slightly more effective than aspirin in preventing vascular events (RR 0.91; 95% CI 0.84–0.97) [319]. It may be more effective in high-risk patients (i.e. those with previous stroke, peripheral artery disease, symptomatic coronary disease, or diabetes) [269].

Dipyridamole

Dipyridamole reduces stroke recurrence with similar efficacy to aspirin [320].

Triflusal

Triflusal reduces stroke recurrence with similar efficacy to aspirin but with fewer adverse events [321].

Dipyridamole plus Aspirin

The combination of aspirin (38–300 mg/day) and dipyridamole (200 mg extended release twice daily) reduces the risk of vascular death, stroke or MI, compared with aspirin alone (RR 0.82; 95% CI 0.74–0.91) [320, 322]. Dipyridamole may cause headache; the incidence of this may be reduced by increasing the dose gradually [323, 324].

Clopidogrel plus Aspirin

Compared with clopidogrel alone, the combination of aspirin and clopidogrel did not reduce the risk of ischaemic stroke, MI, vascular death, or re-hospitalization [325]; however, life-threatening or major bleeding was increased with the combination. Similarly, in the CHARIS-MA study, the combination of aspirin and clopidogrel did not reduce the risk of MI, stroke, or death from CV causes, compared with aspirin alone [269]. In patients who have had an acute coronary event within 12 months, or coronary stenting, the combination of clopidogrel and aspirin reduces the risk of new vascular events [326].

Oral Anticoagulation

Oral anticoagulation after non-cardiac ischaemic stroke is not superior to aspirin, but causes more bleeding [327–329]. Oral anticoagulation (INR 2.0–3.0) reduces the risk of recurrent stroke in patients with non-valvular AF (whether of permanent, chronic or paroxysmal type) [330] and most other cardiac sources of emboli. Anticoagulation should be taken long term, or for at least 3 months after cardioembolic stroke due to MI [331]. There is a controversial discussion about the optimal time point when to start oral anticoagulation. After TIA or minor stroke, one could start immediately, but after major stroke with significant infarction upon neuroimaging (e.g. above a third of the MCA territory) one should wait for some (e.g. 4) weeks. However, this decision has to be individualized.

In patients with AF and stable coronary disease, aspirin should not be added to oral anticoagulation [332]. Anticoagulation may be beneficial in patients with aortic atheroma [333], fusiform aneurysms of the basilar artery [334] or cervical dissection [335]. The ongoing ARCH trial is comparing the combination of clopidogrel plus aspirin with oral anticoagulation in secondary prevention of patients with atherosclerotic plaques in the aortic arch.

Recurrent Vascular Event on Antiplatelet Therapy

The treatment of patients who have a recurrent vascular event on antiplatelet therapy remains unclear. Alternative causes of stroke should be sought and consistent risk-factor management is mandatory especially in those patients. Alternative treatment strategies may be considered: leave unchanged, change to another antiplatelet agent, add another antiplatelet agent, or use oral anticoagulation.

Surgery and Angioplasty

Recommendations

- CEA is recommended for patients with 70–99% stenosis (Class I, Level A). CEA should only be performed in centres with a perioperative complication rate (all strokes and death) of less than 6% (Class I, Level A).
- It is recommended that CEA be performed as soon as possible after the last ischaemic event, ideally within 2 weeks (Class II, Level B).
- It is recommended that CEA may be indicated for certain patients with stenosis of 50–69%; males with very recent hemispheric symptoms are most likely to benefit (Class III, Level C). CEA for stenosis of 50–69% should only be performed in centres with a perioperative complication rate (all stroke and death) of less than 3% (Class I, Level A).
- CEA is not recommended for patients with stenosis of less than 50% (Class I, Level A).
- It is recommended that patients remain on antiplatelet therapy both before and after surgery (Class I, Level A).
- Carotid percutaneous transluminal angioplasty and/or stenting (CAS) is only recommended in selected patients (Class I, Level A). It should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contra-indications to CEA, stenosis at a surgically inaccessible site, re-stenosis after earlier CEA, and post-radiation stenosis (Class IV, GCP). Patients should receive a combination of clopidogrel and aspirin immediately before and for at least 1 month after stenting (Class IV, GCP).
- It is recommended that endovascular treatment may be considered in patients with symptomatic intracranial stenosis (Class IV, GPC).

Carotid Endarterectomy

The grading of stenosis should be performed according to the NASCET criteria. Although ECST (European Carotid Surgery Trialists) and NASCET use different methods of measurement, it is possible to convert the percentage stenosis derived by one method to the other [336]. CEA reduces the risk of recurrent disabling stroke or death (RR 0.52) in patients with severe (70–99%) ipsilateral ICA stenosis [280, 337, 338]. Patients with less severe ipsilateral carotid stenosis (50–69%) may also benefit [338]. Surgery is potentially harmful in patients with mild or moderate degrees of stenosis (<50%) [338].

CEA should be performed as soon as possible (ideally within 2 weeks) after the last cerebrovascular event [339]. Surgical procedure is important in preventing stroke; carotid patch angioplasty may reduce the risk of perioperative arterial occlusion and restenosis [340].

Older patients (>75 years) without organ failure or serious cardiac dysfunction benefit from CEA [339]. Women with severe (>70%) symptomatic stenosis should undergo CEA, whereas women with more moderate stenosis should be treated medically [341]. Patients with amaurosis fugax, severe stenosis and a high risk profile should be considered for CEA; those with amaurosis fugax and few risk factors do better with medical treatment. Patients with mild-to-moderate intracranial stenosis and severe extracranial stenosis should be considered for CEA.

The benefit from CEA is less in patients with lacunar stroke [342]. Patients with leukoaraiosis carry an increased perioperative risk [343]. Occlusion of the contralateral ICA is not a contraindication to CEA but carries a higher perioperative risk. The benefit from endarterectomy is marginal in patients with carotid near-occlusion.

Carotid Angioplasty and Stenting

Several trials have compared CAS and CEA in secondary stroke prevention (table 9) [344–347]. However, the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial included more than 70% asymptomatic patients, and therefore should not be used for decisions about secondary prevention [346]. In CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study), the majority of the patients in the endovascular group underwent angioplasty, and only 26% were treated with a stent [347]. The two most recent studies revealed different results. SPACE (Stent-protected Angioplasty versus Carotid Endarterectomy in symptomatic patients) marginally failed to prove the non-inferiority of CAS compared to CEA; for the endpoint ipsilateral stroke or death up to day 30, the event rates after 1,200 patients were 6.8% for CAS and 6.3% for CEA patients (absolute difference 0.5%; 95% CI –1.9% to 2.9%; p = 0.09) [345]. The French EVA3S (Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis) trial was stopped prematurely after the inclusion of 527 patients because of safety concerns and lack of efficacy. The RR of any stroke or death after CAS, compared with CEA, was 2.5 (95% CI 1.2–5.1) [344]. An updated meta-analysis of these studies revealed a significantly higher risk of any stroke and death within 30 days after CAS, compared with CEA (OR 1.41; 95% CI 1.07–1.87; p = 0.016). However, significant heterogeneity was found in this analysis (p = 0.035) [348]. After the periprocedural period, few ipsilateral strokes occurred with either procedure (table 9).

Intracranial and Vertebral Artery Occlusive Disease

Extracranial-Intracranial Anastomosis

Anastomosis between the superficial temporal and middle cerebral arteries is not beneficial in preventing stroke in patients with MCA or ICA stenosis or occlusion [349].

Table 9. Risk of stroke or death from large-scale randomized trials comparing endovascular and surgical treatment in patients with severe carotid artery stenosis (intention to treat data)

Outcome	Any stroke or death at 30 days		Disabling stroke or death at 30 days		Ipsilateral stroke after 30 days	
	CAS	CEA	CAS	CEA	CAS	CEA
CAVATAS [347]	25 (10.0)	25 (9.9)	16 (6.4)	15 (5.9)	6[1]	10[1]
SAPPHIRE [346]	8 (4.8)	9 (5.4)	unknown	unknown	unknown	unknown
SPACE [345, 584]	46 (7.7)	38 (6.5)	29 (4.8)	23 (3.9)	4 (0.7)[2]	1 (0.2)[2]
EVA3S [344]	25 (9.6)	10 (3.9)	9 (3.4)	4 (1.5)	2 (0.6)[2]	1 (0.3)[2]

Figures in parentheses indicate percentages.
[1] Follow-up duration 1.95 years in mean. [2] Up to 6 months.

Stenting of Intracranial or Vertebral Artery Stenoses

Patients with symptomatic intracranial stenoses of ≥50% are at high risk of recurrent strokes, both in the anterior and posterior circulation (12% after 1 year and 15% after 2 years in the territory of the stenosed artery) [318, 350]. Severe stenoses (≥70%) carry a higher risk than moderate stenoses (50 to <70%) [350]. After stenting, recurrent strokes are reported in about 5–7% of patients with moderate or severe stenoses after 1 year, and in around 8% after 2 years [351, 352]. However, the incidence of complications after either angioplasty or stenting may be up to 6% [353–355]. No randomized controlled trials have evaluated angioplasty, stenting or both for intracranial stenosis. Several non-randomized trials have shown feasibility and acceptable safety of intracranial stenting, but the risk of restenosis remains high [355, 356]. Also stenting of the extracranial segments of the vertebral artery is technically feasible with a moderate periprocedural risk as, for example, demonstrated in the SSYLV1A trial; but especially at the origin, there is a particularly high rate of restenoses [356].

General Stroke Treatment

Recommendations

- Intermittent monitoring of neurological status, pulse, BP, temperature and oxygen saturation is recommended for 72 h in patients with significant persisting neurological deficits (Class IV, GCP)
- It is recommended that oxygen should be administered if the oxygen saturation falls below 95% (Class IV, GCP)
- Regular monitoring of fluid balance and electrolytes is recommended in patients with severe stroke or swallowing problems (Class IV, GCP)
- Normal saline (0.9%) is recommended for fluid replacement during the first 24 h after stroke (Class IV, GCP)
- Routine BP lowering is not recommended following acute stroke (Class IV, GCP)
- Cautious BP lowering is recommended in patients with extremely high BPs (>220/120 mm Hg) on repeated measurements, or with severe cardiac failure, aortic dissection, or hypertensive encephalopathy (Class IV, GCP)
- It is recommended that abrupt BP lowering be avoided (Class II, Level C)
- It is recommended that low BP secondary to hypovolaemia or associated with neurological deterioration in acute stroke should be treated with volume expanders (Class IV, GCP)
- Monitoring serum glucose levels is recommended (Class IV, GCP)
- Treatment of serum glucose levels >180 mg/dl (>10 mM) with insulin titration is recommended (Class IV, GCP)
- It is recommended that severe hypoglycaemia [<50 mg/dl (<2.8 mM)] should be treated with intravenous dextrose or infusion of 10–20% glucose (Class IV, GCP points)
- It is recommended that the presence of pyrexia (temperature >37.5°C) should prompt a search for concurrent infection (Class IV, GCP)
- Treatment of pyrexia (temperature ≥37.5°C) with paracetamol and fanning is recommended (Class III, Level C)
- Antibiotic prophylaxis is not recommended in immunocompetent patients (Class II, Level B)

The term 'general treatment' refers to treatment strategies aimed at stabilizing the critically ill patient in order to control systemic problems that may impair stroke recovery; the management of such problems is a central part of stroke treatment [2, 106]. General treatment includes respiratory and cardiac care, fluid and metabolic management, BP control, the prevention and treatment of conditions such as seizures, venous thromboembolism, dysphagia, aspiration pneumonia, other infections, or pressure ulceration, and occasionally management of elevated intracranial pressure (ICP). However, many aspects of general stroke treatment have not been adequately assessed in randomized clinical trials (RCTs).

It is common practice to actively manage neurological status and vital physiological functions such as BP, pulse, oxygen saturation, blood glucose and temperature. Neurological status can be monitored using validated neurological scales such as the NIH Stroke Scale [104] or the Scandinavian Stroke Scale [357]. There is little direct evidence from RCTs to indicate how intensively monitoring should be carried out, but in stroke unit trials [119] it was common practice to have a minimum of 4-hourly observations for the first 72 h after stroke. Clinical trials using continuous telemetry [358, 359] suggest there may be some benefit from more intensive continuous monitoring in terms of improved detection of complications and reduced length of stay, but clinical outcomes are inconclusive. In practice, more intensive monitoring is often provided for subgroups of patients, such as those with reduced consciousness, progressing neurological deficits, or a history of cardiorespiratory disease. Close monitoring is also required for the first 24 h after thrombolysis. More invasive monitoring procedures, such as central venous catheters or ICP monitoring, are used only in highly selected patient groups.

Pulmonary Function and Airway Protection

Normal respiratory function with adequate blood oxygenation is believed to be important in the acute stroke period to preserve ischaemic brain tissue. However, there is no convincing evidence that routine provision of oxygen at low flow rates to all acute stroke patients is effective [360]. Identification and treatment of hypoxia is believed to be important in individuals with extensive brain stem or hemispheric stroke, seizure activity, or complications such as pneumonia, cardiac failure, pulmonary embolism (PE), or exacerbation of COPD. Blood oxygenation is usually improved by the administration of 2–4 l of oxygen via a nasal tube. Ventilation may be necessary in patients with severely compromised respiratory function. However, before ventilation is performed the general prognosis, coexisting medical conditions, and the presumed wishes of the patient need to be considered.

Cardiac Care

Cardiac arrhythmias, particularly AF, are relatively common after stroke, and heart failure, MI and sudden death are also recognized complications [361, 362]. A significant minority of stroke patients show raised blood troponin levels indicative of cardiac damage [363]. Every stroke patient should have an initial ECG. Cardiac monitoring should be conducted to screen for AF. Optimizing cardiac output with maintenance of high normal BP and a normal heart rate is a standard component of stroke management. The use of inotropic agents is not routine practice, but fluid replacement therapy is commonly used to correct hypovolaemia. Increases in cardiac output may increase cerebral perfusion. Restoration of normal cardiac rhythm using drugs, cardioversion or pacemaker support may occasionally be required.

Fluid Replacement Therapy

Many stroke patients are dehydrated on admission to hospital, and this is associated with a poor outcome [364]. Although clinical trial evidence is limited, delivery of intravenous fluids is commonly considered part of general management of acute stroke, particularly in patients at risk of dehydration due to reduced consciousness or impaired swallowing. Experience in the management of hyperglycaemia supports the avoidance of dextrose in the early post-stroke phase [365]. More specialist fluid replacement therapy with haemodilution has not been shown to improve stroke outcomes [366].

Blood Pressure Management

BP monitoring and treatment is a controversial area in stroke management. Patients with the highest and lowest levels of BP in the first 24 h after stroke are more likely to have early neurological decline and poorer outcomes [367]. A low or low-normal BP at stroke onset is unusual [368], and may be the result of a large cerebral infarct, cardiac failure, ischaemia, hypovolaemia or sepsis. BP can usually be raised by adequate rehydration with crystalloid (saline) solutions; patients with low cardiac output may occasionally need inotropic support. However clinical trials of actively elevating a low BP in acute stroke have yielded inconclusive results.

A systematic review covering a variety of BP-altering agents has not provided any convincing evidence that active management of BP after acute stroke influences patient outcomes [369]. Small studies looking at surrogate markers of cerebral blood flow such as SPECT have indicated that neither perindopril nor losartan lower cerebral blood flow when given within 2–7 days of stroke onset [370]. Several ongoing trials are examining whether BP

should be lowered after acute stroke, and whether antihypertensive therapy should be continued or stopped in the first few days after stroke [371, 372]. In the absence of reliable evidence from clinical trials, many clinicians have developed protocols for the management of extremely high BP. In some centres it is common practice to begin cautious BP reduction when levels exceed 220 mm Hg systolic and 120 mm Hg diastolic. However, in many centres BP reduction is only considered in the presence of severe cardiac insufficiency, acute renal failure, aortic arch dissection, or malignant hypertension. In patients undergoing thrombolysis, it is common practice to avoid systolic BPs above 185 mm Hg.

The use of sublingual nifedipine should be avoided because of the risk of an abrupt decrease in BP [373]. Intravenous labetalol or urapadil are frequently used in North America. Sodium nitroprusside is sometimes recommended.

Blood Glucose Management

Hyperglycaemia occurs in up to 60% of stroke patients without known diabetes [374, 375]. Hyperglycaemia after acute stroke is associated with larger infarct volumes and cortical involvement, and with poor functional outcome [376–378]. There is limited evidence as to whether active reduction of glucose in acute ischaemic stroke improves patient outcomes. The largest randomized trial of blood glucose lowering by glucose potassium insulin infusion [365], compared with standard intravenous saline infusion, found no difference in mortality or functional outcomes in patients with mild-to-moderate blood glucose elevations [median 137 mg/dl (7.6 mM)]. This regime was labour intensive and associated with episodes of hypoglycaemia. At present, the routine use of insulin infusion regimes in patients with moderate hyperglycaemia cannot be recommended. However, it is common practice in stroke units to reduce blood glucose levels exceeding 180 mg/dl (10 mM) [119]. The use of intravenous saline and avoidance of glucose solutions in the first 24 h after stroke is common practice, and appears to reduce blood glucose levels [365].

Hypoglycaemia [<50 mg/dl (2.8 mM)] may mimic an acute ischaemic infarction, and should be treated by intravenous dextrose bolus or infusion of 10–20% glucose [379].

Body Temperature Management

In experimental stroke, hyperthermia is associated with increased infarct size and poor outcome [380]. Raised temperature can be centrally driven or a result of concurrent infection, and is associated with poorer clinical outcomes [381–383]. A raised body temperature should prompt a search for infection and treatment where appropriate. Studies with antipyretic medication have been inconclusive, but treatment of raised body temperature (>37.5°C) with paracetamol is common practice in stroke patients.

Specific Treatment

Recommendations

- Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-min infusion, is recommended within 3 h of onset of ischaemic stroke (Class I, Level A)
- Intravenous rtPA may be of benefit also for acute ischaemic stroke beyond 3 h after onset (Class I, Level B) but is not recommended for routine clinical practice
- The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended for routine clinical practice (Class III, Level C)
- It is recommended that BP of 185/110 mm Hg or higher is lowered before thrombolysis (Class IV, GCP)
- It is recommended that intravenous rtPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischaemia (Class IV, GCP)
- It is recommended that intravenous rtPA may also be administered in selected patients under 18 years and over 80 years of age, although this is outside the current European labelling (Class III, Level C)
- Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option (Class II, Level B)
- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (Class III, Level B). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 h (Class III, Level B)
- It is recommended that aspirin (160–325 mg loading dose) be given within 48 h after ischaemic stroke (Class I, Level A)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 h (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (Class III, Level C)
- The administration of glycoprotein-IIb-IIIa inhibitors is not recommended (Class I, Level A)
- Early administration of unfractionated heparin (UFH), low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischaemic stroke (Class I, Level A)
- Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances (Class I, Level A)

Thrombolytic Therapy

Intravenous Tissue Plasminogen Activator

Thrombolytic therapy with rtPA (0.9 mg/kg body weight, maximum dose 90 mg) given within 3 h after stroke onset significantly improves outcome in patients with acute ischaemic stroke [126]: the NNT to achieve a favourable clinical outcome after 3 months is 7. By contrast, the ECASS (European Cooperative Acute Stroke Study) and ECASS II studies did not show statistically significant superiority of rtPA for the primary endpoints when treatment was given within 6 h [384, 385]. Trials with rtPA, involving a total of 2,889 patients, have shown a significant reduction in the number of patients with death or dependency (OR 0.83; 95% CI 0.73–0.94) [386]. A pooled analysis of individual data of rtPA trials showed that, even within a 3-hour window, earlier treatment results in a better outcome (0–90 min: OR 2.11; 95% CI 1.33–3.55; 90–180 min: OR 1.69; 95% CI 1.09–2.62) [387]. This analysis suggested a benefit up to 4.5 h. Ongoing trials (ECASS III, IST-3) are further investigating the benefits of rtPA beyond 3 h.

The NINDS (National Institute of Neurological Disorders and Stroke) Study showed that the extent of early ischaemic changes (using the ASPECT score) had no effect on treatment response within the 3-hour time window [388]. However, European regulatory agencies do not advocate rtPA treatment in patients with severe stroke (NIHSSS ≥25), extended early ischaemic changes on CT scan, or age above 80 years (unlike the US labelling). Nevertheless, observational studies suggest that rtPA given within 3 h of stroke onset is safe and effective in patients over 80 years of age [389–391], but more randomized data are pending. The effect of gender on the response to rtPA is uncertain [392].

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise and brain CT is assessed by an experienced physician [393–395]. Whenever possible, the risks and benefits of rtPA should be discussed with the patient and family before treatment is initiated.

BP must be below 185/110 mm Hg before, and for the first 24 h after, thrombolysis. Management of high BP is required [126]. Protocol violations are associated with higher mortality rates [396, 397].

Continuous transcranial ultrasound was associated with an increased rate of early recanalization after rtPA in a small randomized trial [398]; this effect may be facilitated by the administration of microbubbles [399]. However, a RCT has recently been stopped for undisclosed reasons.

Intravenous rtPA may be of benefit also for acute ischaemic stroke beyond 3 h after onset, but is not recommended in clinical routine. The use of multimodal imaging criteria may be useful for patient selection. Several large observational studies suggest improved safety and possibly improved efficacy in patients treated with intravenous rtPA beyond 3 h based on advanced imaging findings [131, 160, 400, 401]. However, available data on mismatch, as defined by multimodal MRI or CT, are too limited to guide thrombolysis in routine practice (see also the section on imaging) [153].

Patients with seizures at stroke onset have been excluded from thrombolytic trials because of potential confusion with post-ictal Todd's phenomena. Case series have suggested that thrombolysis may be used in such patients when there is evidence for new ischaemic stroke [389].

Post-hoc analyses have identified the following potential factors associated with increased risk of intracerebral bleeding complications after rtPA use [402]:

- elevated serum glucose
- history of diabetes
- baseline symptom severity
- advanced age
- increased time to treatment
- previous aspirin use
- history of congestive heart failure
- low plasminogen activator inhibitor activity
- NINDS protocol violations.

However, none of these factors reversed the overall benefit of rtPA.

Other Intravenous Thrombolytics

Intravenous streptokinase was associated with an unacceptable risk of haemorrhage and death [403, 404]. Intravenous desmoteplase administered 3–9 h after acute ischaemic stroke in patients selected on the basis of perfusion/diffusion mismatch was associated with a higher rate of reperfusion and better clinical outcome, compared with placebo, in two small RCTs [405, 406]. These findings were not confirmed in the phase III DIAS (Desmoteplase in Acute Ischemic Stroke)-II study, but this agent will be evaluated further.

Intra-Arterial and Combined (IV+IA) Thrombolysis

Intra-arterial thrombolytic treatment of proximal MCA occlusion using pro-urokinase (PUK) within 6 h was significantly associated with better outcome in the PROACT II (Pro-urokinase for Acute Ischemic Stroke)

trial [154]. Additional smaller RCTs with PUK (PROACT I) or urokinase (MELT) and a meta-analysis of PROACT I, PROACT II and MELT indicate a benefit of intra-arterial thrombolytic therapy in patients with proximal MCA occlusions [407]. PUK is not available and intra-arterial thrombolysis with tPA is not substantiated by RCTs, but observational data and non-randomised comparisons are available [155, 408].

A randomized trial comparing standard intravenous rtPA with a combined intravenous and intra-arterial approach (IMS3) has started [409].

Intra-arterial treatment of acute basilar occlusion with urokinase or rtPA has been available for more than 20 years, but has not been tested in an adequately powered RCT [410], although encouraging results have been obtained in observational studies [411, 412]. A systematic analysis found no significant differences between intravenous or intra-arterial thrombolysis for basilar occlusion [413].

Intra-Arterial Recanalization Devices

The MERCI (Mechanical Embolus Removal in Cerebral Embolism) trial evaluated a device that removed the thrombus from an intracranial artery. Recanalization was achieved in 48% (68/141) of patients in whom the device was deployed within 8 h of the onset of stroke symptoms [414]. No RCTs with outcome data are available for any recanalization devices.

Antiplatelet Therapy

The results of two large randomized, non-blinded, intervention studies indicate that aspirin is safe and effective when started within 48 h after stroke [415, 416]. In absolute terms, 13 more patients were alive and independent at the end of follow-up for every 1,000 patients treated. Furthermore, treatment increased the odds of making a complete recovery from the stroke (OR 1.06; 95% CI 1.01–1.11): 10 more patients made a complete recovery for every 1,000 patients treated. Antiplatelet therapy was associated with a small but definite excess of two symptomatic intracranial haemorrhages for every 1,000 patients treated, but this was more than offset by a reduction of seven recurrent ischaemic strokes and about one PE for every 1,000 patients treated.

A randomized, double-blind, placebo-controlled trial showed that aspirin (325 mg), given once daily for 5 consecutive days and starting within 48 h of stroke onset, did not significantly reduce stroke progression, compared with placebo (RR 0.95; 95% CI 0.62–1.45) in patients with incomplete paresis [417].

The use of clopidogrel, dipyridamole, or combinations of oral antiplatelet agents in acute ischaemic stroke has not been evaluated.

In a double-blind phase II, the glycoprotein-IIb-IIIa inhibitor abciximab produced a non-significant shift in favourable outcomes, as measured by modified Rankin scores (mRS) at 3 months, compared with placebo (OR 1.20; 95% CI 0.84–1.70) [418]. A phase III study evaluating the safety and efficacy of abciximab was terminated prematurely after 808 patients had been enrolled because of an increased rate of symptomatic or fatal intracranial bleeding with abciximab compared to placebo (5.5 vs. 0.5%; $p = 0.002$). This trial also did not demonstrate an improvement in outcomes with abciximab [419].

Early Anticoagulation

Subcutaneous UFH at low or moderate doses [415], nadroparin [420, 421], certoparin [422], tinzaparin [423], dalteparin [424] and intravenous danaparoid [425] have failed to show an overall benefit of anticoagulation when initiated within 24–48 h from stroke onset. Improvements in outcome or reductions in stroke recurrence rates were mostly counterbalanced by an increased number of haemorrhagic complications. In a meta-analysis of 22 trials, anticoagulant therapy was associated with about nine fewer recurrent ischaemic strokes per 1,000 patients treated (OR 0.76; 95% CI 0.65–0.88), and with about nine more symptomatic intracranial haemorrhages per 1,000 (OR 2.52; 95% CI 1.92–3.30) [426]. However, the quality of the trials varied considerably. The anticoagulants tested were standard UFH, low molecular weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors.

Few clinical trials have assessed the risk-benefit ratio of very early administration of UFH in acute ischaemic stroke. In one study, patients with nonlacunar stroke anticoagulated within 3 h had more self-independence (38.9 vs. 28.6%; $p = 0.025$), fewer deaths (16.8 vs. 21.9%; $p = 0.189$), and more symptomatic brain haemorrhages (6.2 vs. 1.4%; $p = 0.008$) [427]. In the RAPID (Rapid Anticoagulation Prevents Ischemic Damage) trial, patients allocated UFH had fewer early recurrent strokes and a similar incidence of serious haemorrhagic events, compared with those receiving aspirin [428]. In the UFH group, ischaemic or haemorrhagic worsening was associated with inadequate plasma levels of UFH. In view of these

findings, the value of UFH administered shortly after symptom onset is still debated [429, 430].

RCTs have not identified a net benefit of heparin for any stroke subtype. A meta-analysis restricted to patients with acute cardioembolic stroke showed that anticoagulants given within 48 h of clinical onset were associated with a non-significant reduction in recurrence of ischaemic stroke, but no substantial reduction in death or disability [431]. Despite this lack of evidence, some experts recommend full-dose heparin in selected patients, such as those with cardiac sources of embolism with high risk of re-embolism, arterial dissection or high-grade arterial stenosis prior to surgery. Contraindications for heparin treatment include large infarcts (e.g. more than 50% of MCA territory), uncontrollable arterial hypertension and advanced microvascular changes in the brain.

Neuroprotection

No neuroprotection programme has shown improved outcome on its predefined primary endpoint. Recent RCTs with the free radical trapping agent NXY-059 [432], and magnesium sulphate [433] were negative. A randomized, placebo-controlled, phase III trial of intravenous rtPA followed by antioxidant therapy with uric acid is ongoing, following a safe phase II study [434]. A meta-analysis has suggested a mild benefit with citocoline [435]; a clinical trial with this agent is in progress.

Brain Oedema and Elevated Intracranial Pressure

Recommendations

- Surgical decompressive therapy within 48 h after symptom onset is recommended in patients up to 60 years of age with evolving malignant MCA infarcts (Class I, Level A)
- It is recommended that osmotherapy can be used to treat elevated ICP prior to surgery if this is considered (Class III, Level C)
- No recommendation can be given regarding hypothermic therapy in patients with space-occupying infarctions (Class IV, GCP)
- It is recommended that ventriculostomy or surgical decompression be considered for treatment of large cerebellar infarctions that compress the brainstem (Class III, Level C)

Space-occupying brain oedema is a main cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening brain oedema usually develops between the 2nd and 5th day after stroke onset, but up to a third of patients can have neurological deterioration within 24 h after symptom onset [436, 437].

Medical Therapy

Medical therapy in patients with large space-occupying infarctions and brain oedema is based mostly on observational data. Basic management includes head positioning at an elevation of up to 30°, avoidance of noxious stimuli, pain relief, appropriate oxygenation and normalizing body temperature. If ICP monitoring is available, cerebral perfusion pressure should be kept above 70 mm Hg [438]. Intravenous glycerol (4 × 250 ml of 10% glycerol over 30–60 min) or mannitol (25–50 g every 3–6 h) is first line medical treatment if clinical or radiological signs of space-occupying oedema occur [439, 440]. Intravenous hypertonic saline solutions are probably similarly effective [441]. Hypotonic and glucose-containing solutions should be avoided as replacement fluids. Dexamethasone and corticosteroids are not useful [442]. Thiopental given as a bolus can quickly and significantly reduce ICP, and can be used to treat acute crises. Barbiturate treatment requires ICP and electroencephalography (EEG) monitoring and careful haemodynamic monitoring, as a significant BP drop may occur.

Hypothermia

Mild hypothermia (i.e. brain temperature between 32–33°C) reduces mortality in patients with severe MCA infarcts, but may cause severe side effects including recurrent ICP crisis during re-warming [443, 444]. In a small RCT, mild hypothermia (35°C) in addition to decompressive surgery produced a trend towards a better clinical outcome than decompressive surgery alone ($p = 0.08$) [445].

Decompressive Surgery

Malignant MCA Infarction

A pooled analysis of 93 patients included in the DECIMAL (decompressive craniectomy in malignant MCA infarcts), DESTINY (decompressive surgery for the treatment of malignant infarction of the MCA), and HAMLET (hemicraniectomy after MCA infarction with life-threatening edema trial) trials showed that, compared with the control group, at 1 year more patients in the decompressive surgery group had an mRS ≤4 or mRS ≤3, and more survived (NNTs 2, 4 and 2, respectively) [446, 447]. There was no increase in the proportion of patients who survived surgery in a vegetative stage (mRS 5). Inclusion criteria for this combined analysis were age 18–60 years, NIHSSS >15, decrease in level of consciousness to

a score of 1 or greater on item 1a of the NIHSS, infarct signs on CT of 50% or more of the MCA territory or >145 cm^3 on DWI, and inclusion <45 h after onset (surgery <48 h). Follow-up of survival and functional status beyond 1 year is currently ongoing in the DECIMAL and DESTINY studies [447].

A systematic review of 12 observational retrospective studies found age above 50 years to be a predictor of poor outcome. The timing of surgery, side of infarction, clinical signs of herniation before surgery, and involvement of other vascular territories did not significantly affect outcome [448].

Cerebellar Infarction

Ventriculostomy and decompressive surgery are considered treatments of choice for space-occupying cerebellar infarctions, although RCTs are lacking. As in space-occupying supratentorial infarction, the operation should be performed before signs of herniation are present. The prognosis among survivors can be very good, even in patients who are comatose before surgery.

Prevention and Management of Complications

Recommendations

- It is recommended that infections after stroke should be treated with appropriate antibiotics (Class IV, GCP).
- Prophylactic administration of antibiotics is not recommended, and levofloxacin can be detrimental in acute stroke patients (Class II, Level B).
- Early rehydration and graded compression stockings are recommended to reduce the incidence of venous thromboembolism (Class IV, GCP).
- Early mobilization is recommended to prevent complications such as aspiration pneumonia, DVT and pressure ulcers (Class IV, GCP).
- It is recommended that low-dose subcutaneous heparin or low molecular weight heparins should be considered for patients at high risk of DVT or PE (Class I, Level A).
- Administration of anticonvulsants is recommended to prevent recurrent post-stroke seizures (Class I, Level A). Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended (Class IV, GCP).
- An assessment of falls risk is recommended for every stroke patient (Class IV, GCP).
- Calcium/vitamin D supplements are recommended in stroke patients at risk of falls (Class II, Level B).
- Bisphosphonates (alendronate, etidronate and risedronate) are recommended in women with previous fractures (Class II, Level B).
- In stroke patients with urinary incontinence, specialist assessment and management is recommended (Class III, Level C).
- Swallowing assessment is recommended but there are insufficient data to recommend a specific approach for treatment (Class III, GCP).
- Oral dietary supplements are only recommended for non-dysphagic stroke patients who are malnourished (Class II, Level B).
- Early commencement of nasogastric (NG) feeding (within 48 h) is recommended in stroke patients with impaired swallowing (Class II, Level B).
- It is recommended that percutaneous enteral gastrostomy (PEG) feeding should not be considered in stroke patients in the first 2 weeks (Class II, Level B).

Aspiration and Pneumonia

Bacterial pneumonia is one of the most important complications in stroke patients [449], and is mainly caused by aspiration [450]. Aspiration is frequently found in patients with reduced consciousness and in those with swallowing disturbances. Oral feeding should be withheld until the patient has demonstrated intact swallowing with small amounts of water and intact coughing on command. NG or PEG feeding may prevent aspiration pneumonia, although reflux of liquid feed, hypostasis, diminished cough and immobilization increase the risk. Frequent changes of the patient's position in bed and pulmonary physical therapy may prevent aspiration pneumonia. A brain-mediated immunodepressive state contributes to post-stroke infection [451, 452]. Prophylactic administration of levofloxacin (500 mg/100 ml/day for 3 days) is not better than optimal care for the prevention of infection in patients with nonseptic acute stroke and was inversely associated with outcome at day 90 (OR 0.19; 95% CI 0.04 to 0.87, p = 0.03) [453].

Deep Vein Thrombosis and Pulmonary Embolism

It is generally accepted that the risk of DVT and PE can be reduced by early hydration and early mobilization. Although graded compression stockings are effective in preventing venous thromboembolism in surgical patients, their efficacy after stroke is unproven [454]. In stroke patients, low-dose LMWH reduced the incidence of both DVT (OR 0.34; 95% CI 0.19–0.59) and PE (OR 0.36; 95% CI 0.15–0.87), without an increased risk of intracerebral (OR 1.39; 95% CI 0.53–3.67) or extracerebral haemorrhage (OR 1.44; 95% CI 0.13–16), NNT: 7 and 38 for DVT and PE, respectively, while low-dose UFH decreased the thrombosis risk (OR 0.17; 95% CI 0.11–0.26), but had no influence on PE (OR 0.83, 95% CI 0.53–1.31);

the risk of ICH was not statistically significantly increased (OR 1.67; 95% CI 0.97–2.87) [455]. Nevertheless, prophylaxis with subcutaneous low-dose heparin (5,000 IU twice daily) or low molecular weight heparins is indicated in patients at high risk of DVT or PE (e.g. due to immobilization, obesity, diabetes, previous stroke) [456, 457].

Pressure Ulcer

In patients at high risk of developing pressure ulcers, use of support surfaces, frequent repositioning, optimizing nutritional status, and moisturizing sacral skin are appropriate preventive strategies [458]. The skin of the incontinent patient must be kept dry. For patients at particularly high risk, an air-filled or fluid-filled mattress system should be used.

Seizures

Partial or secondary generalized seizures may occur in the acute phase of ischaemic stroke. Standard anti-epileptic drugs should be used based on general principles of seizure management. There is no evidence that primary prophylactic anticonvulsive treatment is beneficial.

Agitation

Agitation and confusion may be a consequence of acute stroke, but may also be due to complications such as fever, volume depletion or infection. Adequate treatment of the underlying cause must precede any type of sedation or antipsychotic treatment.

Falls

Falls are common (up to 25%) after stroke in the acute setting [459], during in-patient rehabilitation [460], and in the long term [461]. Likely risk factors for falls in stroke survivors [462] include cognitive impairment, depression, polypharmacy and sensory impairment [463, 464]. A multidisciplinary prevention package that focuses on personal and environmental factors has been found to be successful in general rehabilitation settings [465, 466]. There is a 5% incidence of serious injury [459], including hip fractures (which are fourfold more common than in age-matched controls [467]), which is associated with poor outcome [468]. Exercise [469], calcium supplements [470] and bisphosphonates [471] improve bone strength and decrease fracture rates in stroke patients. Hip protectors can reduce the incidence of fracture for high-risk groups in institutional care, but evidence is less convincing for their use in a community setting [472].

Urinary Tract Infections and Incontinence

The majority of hospital-acquired urinary tract infections are associated with the use of indwelling catheters [473, 474]. Intermittent catheterization has not been shown to reduce the risk of infection. Once urinary infection is diagnosed, appropriate antibiotics should be chosen: to avoid bacterial resistance developing, prophylactic antibiotics are best avoided.

Urinary incontinence is common after stroke, particularly in older, more disabled and cognitively impaired patients [475]. Recent estimates suggest a prevalence of 40–60% in an acute stroke population, of whom 25% are still incontinent at discharge and 15% remain incontinent at 1 year [476]. Urinary incontinence is a strong predictor of poor functional outcome, even after correcting for age and functional status [477]. However, data from the available trials are insufficient to guide continence care of adults after stroke [474, 478]. However, there is suggestive evidence that professional input through structured assessment and management of care and specialist continence nursing may reduce urinary incontinence and related symptoms after stroke. Structured assessment and physical management have been shown to improve continence rates in both inpatients and outpatients [474, 476]. However, trials of interventions are insufficient in number and quality to make any recommendations [478].

Dysphagia and Feeding

Oropharyngeal dysphagia occurs in up to 50% of patients with unilateral hemiplegic stroke [479]. The prevalence of dysphagia is highest in the acute stages of stroke, and declines to around 15% at 3 months [480]. Dysphagia is associated with a higher incidence of medical complications and increased overall mortality [479].

Withholding or limiting oral intake can worsen the catabolic state that may be associated with an acute illness such as stroke. Estimates of the incidence of malnu-

trition vary from 7–15% at admission [481, 482] and 22–35% at 2 weeks [483]. Among patients requiring prolonged rehabilitation, the prevalence of malnutrition may reach 50% [484]. Malnutrition predicts a poor functional outcome [485] and increased mortality [486, 487]. However, routine supplementation for all acute stroke patients did not improve outcomes or reduce complications [488]. There are no adequately powered trials of targeting supplementation to stroke patients at high risk of malnutrition.

For patients with continuing dysphagia, options for enteral nutrition include NG or PEG feeding. A trial of early (median 48 h after stroke) versus delayed (1 week) NG feeding found no significant benefit of early feeding, although there was a trend to fewer deaths in the early NG group [488]. In a related trial examining PEG and NG feeding within 30 days, PEG feeding was no better than NG and in fact was potentially harmful [488]. PEG feeding has also been studied in longer-term dysphagia. Two trials comparing PEG and NG feeding found a trend towards improved nutrition with PEG feeding that did not reach statistical significance [489, 490]. Studies that have addressed quality of life found it was not improved by PEG feeding [491, 492].

Rehabilitation

Even with optimal stroke unit care including thrombolysis, fewer than one third of patients recover fully from stroke [387]. Rehabilitation aims to enable people with disabilities to reach and maintain optimal physical, intellectual, psychological and/or social function [493]. Goals of rehabilitation can shift from initial input to minimize impairment to more complex interventions designed to encourage active participation.

Setting for Rehabilitation

Recommendations

- Admission to a stroke unit is recommended for acute stroke patients to receive coordinated multidisciplinary rehabilitation (Class I, Level A)
- Early initiation of rehabilitation is recommended (Class III, Level C)
- It is recommended that early discharge from stroke unit care is possible in medically stable patients with mild or moderate impairment providing that rehabilitation is delivered in the community by a multidisciplinary team with stroke expertise (Class I, Level A)
- It is recommended to continue rehabilitation after discharge during the first year after stroke (Class II, Level A)
- It is recommended to increase the duration and intensity of rehabilitation (Class II, Level B)

A key characteristic of stroke units is rehabilitation delivered by a specialized multidisciplinary team [494]. The Stroke Unit Trialists' Collaboration [61] has shown improved survival and functional outcomes for patients treated in a dedicated stroke ward, and there are also long-term functional benefits of dedicated stroke unit care; follow-up at 5 and 10 years has revealed persisting efficacy compared with controls [495, 496]. The financial and social implications of prolonged hospitalization have prompted increasing interest in services to facilitate early return to the community. A multidisciplinary early supported discharge team with stroke expertise, comprising (at least) nursing, physiotherapy and OT, can significantly reduce bed days for selected stroke patients [497] who have mild or moderate impairment at baseline [498]. However, specialist discharge services are required: mortality was substantially increased when patients were discharged early with only generic community support [499].

A meta-analysis showed that continued rehabilitation after discharge during the 1st year after stroke reduces the risk of deterioration in function and improves activities of daily living (ADL) [500]. The interventions included OT, physiotherapy, and multidisciplinary teams, and therefore no definitive statement can be made concerning the optimal mode of service delivery.

Timing, Duration and Intensity of Rehabilitation

The optimal timing of rehabilitation is unclear. Proponents of early therapy cite evidence from functional neuroimaging [501] and animal studies [502, 503] that define the peri-infarct period as the crucial time to begin rehabilitation. Early initiation of rehabilitation is a key component of stroke unit care [61] but there is a lack of consensus on the definition of 'early therapy'. Trials comparing 'early' and 'late' initiation of rehabilitation have reported improved prognosis if therapy is started within 20–30 days [504, 505]. Many of the immediate complications of stroke (DVT, skin breakdown, contracture formation, constipation, and hypostatic pneumonia) are related to immobility [506], and hence mobilization is a fundamental component of early rehabilitation. The optimal timing of first mobilization is unclear, but mobilization within the first few days appears to be well toler-

ated [507]. Preliminary results from the ongoing AVERT study of rehabilitation within 24 h suggest that immediate physical therapy is well tolerated with no increase in adverse events [508].

There are few studies of rehabilitation beyond a year after the acute event, and data are inconclusive to make a recommendation on rehabilitation in this phase [509].

Greater intensity of rehabilitation, especially time spent working on ADL, is associated with improved functional outcomes [510, 511]. A systematic review of rehabilitation therapies for improving arm function also suggests a dose-response relationship, although heterogeneity of included studies precluded a formal measure of effect size [512]. Greatest benefits were observed in studies of lower limb exercises and general ADL training.

Organisation and 'quality' of care may be more important than absolute hours of therapy [513]. In a comparison between a dedicated stroke multidisciplinary team and usual ward-based rehabilitation, the dedicated team achieved better outcomes with significantly fewer hours of therapy [514].

Elements of Rehabilitation

Recommendations

- Physiotherapy is recommended, but the optimal mode of delivery is unclear (Class I, Level A)
- Occupational therapy is recommended, but the optimal mode of delivery is unclear (Class I, Level A)
- While assessment for communication deficits is recommended, there are insufficient data to recommend specific treatments (Class III, GCP)
- It is recommended that information is provided to patient and carers but evidence does not support use of a dedicated stroke liaison service for all patients (Class II, Level B)
- It is recommended that rehabilitation be considered for all stroke patients, but there is limited evidence to guide appropriate treatment for the most severely disabled (Class II, Level B)
- While assessment for cognitive deficits appears desirable, there are insufficient data to recommend specific treatments (Class I, Level A)
- It is recommended that patients be monitored for depression during hospital stay and throughout follow-up (Class IV, Level B)
- Drug therapy and non-drug interventions are recommended to improve mood (Class I, Level A)
- Drug therapy should be considered to treat post-stroke emotionalism (Class II, Level B)
- Tricyclic or anticonvulsant therapy is recommended to treat post-stroke neuropathic pain in selected patients (Class III, Level B)
- It is recommended that botulinum toxin be considered to treat post-stroke spasticity, but functional benefits are uncertain (Class III, Level B)

The results from stroke unit trials favour coordinated multidisciplinary teams of staff with expertise in stroke care [515]. The composition of these teams is not formally prescribed, but usually includes stroke physicians, nursing staff, physiotherapists, occupational therapists, and speech and language therapists.

Physiotherapy

There is no clearly superior model of physiotherapy for stroke rehabilitation [516, 517], but some evidence exists to support specific interventions. Several groups have shown that strength can be improved in a dose-dependent manner, without increasing spasticity [512]. Functional electrical stimulation may increase strength, but the effect on clinically relevant outcomes is uncertain [518].

A systematic review did not demonstrate efficacy of treadmill training to improve walking [519]. Electromechanical gait training in combination with physical therapy may be more effective than physiotherapy alone [520]. There are limited data to support the widespread use of orthoses and assistive devices [521].

CV fitness can deteriorate during the recovery phase of a stroke. This physical deconditioning impairs active rehabilitation and is a risk marker for further events [522]. Meta-analysis has shown that aerobic training can improve exercise capacity in individuals with mild to moderate motor deficit after stroke [469].

Constraint-induced movement therapy involves intensive task-orientated exercise of the paretic limb, with restraint of the non-paretic limb. The EXCITE study reported positive results for this method 3–9 months after stroke in a group of medically stable stroke survivors, with some arm movement benefit persisting at 1 year [523].

Occupational Therapy

A systematic review of nine trials comparing OT-based ADL therapy with usual care reported improved functional outcomes in the active intervention group [524]. The data do not justify conclusions on the optimal mode of OT delivery.

A meta-analysis of community-based OT trials found improved performance on ADL measures. The greatest effects were seen in older patients and with the use of

targeted interventions [525]. Specific leisure-based OT therapies did not translate into improved ADL. A trial of providing OT intervention to care home residents after stroke found less functional deterioration in the active intervention group [526]. No controlled trial data describe the effectiveness of OT beyond 1 year after stroke.

Speech and Language Therapy

SLT may optimize safe swallowing, and may assist communication. Two trials of formal SLT input for dysphagia found no significant difference to usual care [527]. A study comparing simple written instruction to graded levels of speech and language intervention for dysphagia found no difference in outcomes between the groups [528].

Aphasia and dysarthria are common symptoms after stroke, and impact on quality of life [529]. A systematic review of SLT for dysarthria in non-progressive brain damage (stroke and head injury) found no good-quality evidence for benefit [530]. Similarly, a systematic review of SLT for aphasia [531] reported insufficient good-quality evidence to recommend formal or informal interventions. The studies included in this review were community based and had an average time to therapy of 3 months: they offer little to inform acute ward-based rehabilitation. Two related meta-analyses of studies with weaker design concluded that improvement in speech is greater if SLT is initiated early [532, 533]. Limited evidence supports the possible use of modified constraint-induced therapy for patients with aphasia [534, 535].

Stroke Liaison and Information Provision

A recent systematic review comparing dedicated stroke liaison to usual care found no evidence of improvement in ADL, subjective health status or carers' health [536]. On subgroup analysis, success of a stroke liaison service was predicted by younger age, less severe deficit, and an emphasis on education within the service.

Inadequate provision of information is predictive of poor quality of life in stroke patients and their families [537]. There is some evidence that combining information with educational sessions improves knowledge and is more effective than providing information alone [538]. As the patient progresses from hospital-based rehabilitation to the community, involvement of carers in rehabilitation becomes increasingly important. Formal training of caregivers in delivery of care reduces personal costs and improves quality of life [539].

Other Groups

Depending on patient-specific goals, input from various other therapists may be appropriate. Such groups include dieticians, orthoptists and social workers. Although there has been limited formal research in this area, some authors have argued that dedicated staffing creates an 'enriched environment' that encourages practice in rehabilitation activities outside periods of formal therapy [540].

Cognitive Deficits

Cognitive deficits are common following stroke and impact on quality of life. At present, there is no evidence for the efficacy of specific memory rehabilitation [541]. Cognitive training for attention deficit has not resulted in meaningful clinical improvement in ADL measures [542]. Training for spatial neglect has improved impairment measures, but an effect on ADL performance has not been demonstrated [543]. A few studies have assessed rehabilitation training strategies in visual inattention and apraxia: no specific conclusions can be drawn [544].

Sexuality

Sexuality can suffer after a stroke. Underlying physical limitations and comorbid vascular disease may be compounded by side effects of medications [545]. It may be desirable to discuss issues of sexuality and intimacy with patients [546]. Provision of support and information is important: many patients wrongly fear that resuming an active sex life may result in further stroke [547].

Complications Affecting Rehabilitation

Rehabilitation can be compromised by complications, which may be strong predictors of poor functional outcome and mortality. Common complications during inpatient rehabilitation include depression, shoulder pain, falls, urinary disturbances and aspiration pneumonia [548]. Some of these are discussed under 'Prevention and Management of Complications'.

Post-Stroke Depression

Post-stroke depression is associated with poor rehabilitation results and ultimately poor outcome [549, 550].

In clinical practice, only a minority of depressed patients are diagnosed and even fewer are treated [551]. Depression has been reported in up to 33% of stroke survivors, compared with 13% of age- and sex-matched controls [552], but reliable estimates of the incidence and prevalence of depression in a stroke cohort are limited [550]. Predictors of post-stroke depression in the rehabilitation setting include increasing physical disability, cognitive impairment and stroke severity [550]. There is no consensus on the optimal method for screening or diagnosis of post-stroke depression. Standard depression screening tools may be inappropriate for patients with aphasia or cognitive impairment [553, 554].

Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) and heterocyclics can improve mood after stroke [555, 556], but there is less evidence that these agents can effect full remission of a major depressive episode or prevent depression. SSRIs are better tolerated than heterocyclics [557]. There is no good evidence to recommend psychotherapy for treatment or prevention of post-stroke depression [558], although such therapy can elevate mood. There is a lack of robust evidence regarding the effect of treating post-stroke depression on rehabilitation or functional outcomes.

Emotionalism is a distressing symptom for patients and carers. SSRIs may reduce emotional outbursts but effects on quality of life are not clear [559].

Pain and Spasticity

Post-stroke shoulder pain is common [560], especially in patients with impaired arm function and poor functional status, and is associated with poorer outcome. Passive movement of a paretic limb may be preventive [561]. Electrical stimulation is commonly used for treatment, but its efficacy is unproven [562]. A Cochrane systematic review found insufficient data to recommend the use of orthotic devices for shoulder subluxation, despite a trend towards efficacy for arm strapping of the affected limb [563].

Lamotrigine and gabapentin may be considered for neuropathic pain [564]. They appear to be well tolerated, but cognitive side effects should be considered.

Spasticity in the chronic phase may adversely affect ADL and quality of life [565]. Posture and movement therapy, relaxing therapy, splints and supports are all commonly employed, but a sound evidence base is lacking [566]. Pharmacotherapy with botulinum toxin has proven effects on muscle tone in arms and legs, but functional benefits are less well studied [567–569]. Oral agents are limited in their use because of side effects [570].

Eligibility for Rehabilitation

An important predictor of rehabilitation outcome is initial stroke severity [549]. Pre-stroke disability is clearly also a strong determinant of outcome [571]. Other factors, such as sex [572], stroke aetiology [573], age [574] and topography of lesion [575], have all been studied as potential predictors of rehabilitation outcome; however, there is no evidence that these non-modifiable factors should influence decisions on rehabilitation [576]. Admission to a dedicated stroke unit improves outcomes for all strokes irrespective of age, sex and severity [61].

Exclusion from rehabilitation on the basis of pre-stroke dependence remains a contentious issue [577, 578]. Patients with the most severe cognitive or physical impairments have been excluded from most rehabilitation trials, and therefore caution is required in extrapolating results to this group [579]. Limited data suggest that active rehabilitation allows severely disabled patients to return home [580, 581]. For those unable to participate actively, passive movements to prevent contractures or pressure sores have been recommended [2].

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Appendix

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Preventive Antibacterial Therapy in Acute Ischemic Stroke: A Randomized Controlled Trial

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Abstract

Background: Pneumonia is a major risk factor of death after acute stroke. In a mouse model, preventive antibacterial therapy with moxifloxacin not only prevents the development of post-stroke infections, it also reduces mortality and improves neurological outcome significantly. In this study we investigate whether this approach is effective in stroke patients.

Methods: Preventive ANtibacterial THERapy in acute Ischemic Stroke (PANTHERIS) is a randomized, double-blind, placebo-controlled trial in 80 patients with severe, non-lacunar, ischemic stroke (NIHSS>11) in the middle cerebral artery (MCA) territory. Patients received either intravenous moxifloxacin (400 mg daily) or placebo for 5 days starting within 36 hours after stroke onset. Primary endpoint was infection within 11 days. Secondary endpoints included neurological outcome, survival, development of stroke-induced immunodepression, and induction of bacterial resistance.

Findings: On intention-to treat analysis (79 patients), the infection rate at day 11 in the moxifloxacin treated group was 15.4% compared to 32.5% in the placebo treated group ($p = 0.114$). On per protocol analysis ($n = 66$), moxifloxacin significantly reduced infection rate from 41.9% to 17.1% ($p = 0.032$). Stroke associated infections were associated with a lower survival rate. In this study, neurological outcome and survival were not significantly influenced by treatment with moxifloxacin. Frequency of fluoroquinolone resistance in both treatment groups did not differ. On logistic regression analysis, treatment arm as well as the interaction between treatment arm and monocytic HLA-DR expression (a marker for immunodepression) at day 1 after stroke onset was independently and highly predictive for post-stroke infections.

Interpretation: PANTHERIS suggests that preventive administration of moxifloxacin is superior in reducing infections after severe non-lacunar ischemic stroke compared to placebo. In addition, the results emphasize the "pivotal" role of immunodepression in developing post-stroke infections.

Trial Registration: Controlled-Trials.com ISRCTN74386719

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Competing Interests: HH, AM, KP, UD, EH, SB, and CM received speakers' honoraria from Bayer Vital GmbH. A patent application on anti-infective agents and immunmodulators used for preventive therapy following an acute cerebrovascular accident has been filed to the European Patent Office (PCT/EP08/02246); Patent owner: Charité Universitaetsmedizin Berlin; Patent inventors: AM, CM, KP, EH, UD.

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Introduction

The prognosis of stroke mainly depends on the incidence of complications [1,2]. Stroke-associated pneumonia, occurring in 7 to 22% [3], is one of the main severe complications [4,5] and thought to be the most common cause of poor outcome and death in stroke patients [6–8]. The risk for pneumonia is highest in the acute state of stroke [9] and in patients with non-lacunar strokes in the MCA territory [7]. Several risk factors contribute to the increased susceptibility of stroke patients for infections: aspiration due to drowsiness, impaired bulbar reflexes, dysphagia, and hypostasis in bed-ridden patient's, as well as the need for invasive

medical procedures [10]. Recently, we demonstrated in a mouse stroke model that infections and mortality can effectively be reduced, and neurological outcome improved by preventive antibacterial therapy with the fluoroquinolone antibiotic moxifloxacin [11]. Based on these findings we designed the PANTHERIS trial to investigate whether preventive antibacterial short-term therapy (PAT) reduces the incidence of infections compared to the current standard therapy. In an explorative fashion we tested whether PAT also reduces mortality and improves neurological outcome. To evaluate the safety of the proposed preventive regimen of treatment we tested whether PAT promotes resistance among facultative pathogenic bacteria. Finally, we seek for underlying immunological mechanisms of increased infectious susceptibility after stroke.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

This investigator initiated study was designed as a randomized, double-blind, placebo-controlled trial in two academic centers (Charité Campus Mitte, Charité Campus Benjamin Franklin) and one community hospital (Unfallkrankenhaus Berlin), and was conducted between May 2003 and July 2006. The protocol was approved by the local ethics committee. Informed consent was obtained from the patient or their legal guardian. PANTHERIS was registered with ISRCTN74386719 at Current Controlled Trials (http://www.controlled-trials.com/ISRCTN74386719). Data safety was independently monitored and audited by local monitoring authorities (Koordinationszentrum für klinische Studien, KKS Charité). Study entry criteria were the occurrence of an acute ischemic stroke (between 9 and 36 h after onset) in the MCA territory with a score of at least 12 on the National Institute of Health Stroke Scale (NIHSS), and patient age of at least 18 years. Exclusion criteria were: hemorrhagic stroke, clinical signs of infection on admission, contraindications against moxifloxacin, preceding or ongoing antibiotic therapy within the last 24 h, participation in another interventional trial, or immunosuppressant treatment within the last 30 days. In order to avoid inclusion of lacunar strokes, only patients with signs of cortical involvement (e.g. aphasia, neglect) or with disturbances of consciousness in addition to hemiparesis were included if initial CT scan was negative for signs of ischemic stroke. We used a computer generated allocation schedule. Because of the greater number of strata, an adaptive randomization was adopted, including sex, affected MCA territory, age (≤64 vs. >64), and center as stratifying factors [12]. Trial pharmacists in each site labelled the trial drugs with sequential study numbers according to randomisation lists prepared by the trial statistician and dispensed the drugs. Study investigators and enrolling staff were masked to the assignment.

Patients were randomly assigned to receive a daily iv infusion over 60 minutes either verum [n = 40, moxifloxacin 400 mg/250 mL solution for infusion (Avalox®, Bayer Vital GmbH)] or placebo [n = 40, riboflavin as a colorant, 20 mg/250 mL NaCl 0.9%] for five days starting within 36h after stroke onset. Verum and placebo medication were visually indistinguishable. In case of an intercurrent infection warranting treatment, in both groups the study medication was continued and supplemented by a treatment following predefined schemes: Treatment of 1) pneumonia: 3×1 g/d iv ceftazidime and 1×5 mg/kg bw/d iv tobramycin; 2) endocarditis/bacteriemia: 2×1g/d iv vancomycin 3) urinary tract infections: 2×400 mg iv ciprofloxacin. However, when infections were refractory to therapy, study medication could be discontinued, and treatment could be adapted following medical reasoning.

After admission all patients underwent cranial CT scanning to exclude intracranial hemorrhage. Patients were treated on stroke units according to recommendations of the European stroke initiative [13]. C-reactive protein was measured daily. Neurological diagnostic work up aimed at identification of stroke cause, which was classified following TOAST criteria [14]. Comorbidity factors were recorded. Neurological deficit was measured at admission and on days 2, 6, and 11 using NIHSS [15].

Primary endpoint was the infection rate within 11 days after stroke onset. The day when infection occurred refers to the day after stroke onset and not study treatment initiation. Infections were diagnosed according to modified criteria of the U.S. Centers for Disease Control and Prevention (CDC): Pneumonia was diagnosed when at least one of the first and one of the latter criteria were fulfilled: A) abnormal respiratory examination, pulmonary infiltrates in chest x-rays; B) productive cough with purulent sputum, microbiological cultures from lower respiratory tract or blood cultures, leukocytosis, and elevation of C-reactive protein (CRP). Diagnosis of urinary tract infection (UTI) was based on two of the following criteria: fever (>38·0°C), urine sample positive for nitrite, leucocyturia, and significant bacteriuria. Secondary endpoint measures were survival and functional outcome (Barthel Index [16]; BI) at day 180 after stroke. BI was dichotomized into good (BI≥60) and bad outcomes (BI<60).

Quantitative or semiquantitative cultures from lower respiratory tract (sputum, tracheobronchial or bronchoalveolar lavage), urine, and blood cultures (BacT/Alert FA aerobic and anaerobic bottles, Biomerieux, INC. Durham, NC 27704, USA) were performed in each case of infection. Urine samples were obtained from previously inserted urinary catheters. Significant bacteriuria was considered when $>10^4$ cfu/mL of a uropathogen were isolated. Quantitative cultures of bronchoalveolar lavage or tracheobronchial samples have used a diagnostic threshold of $>10^6$ cfu/mL and of $>10^5$ cfu/mL, respectively. Species identification and antimicrobial susceptibility testing (microbroth dilution test) followed standard operating procedures according to Clinical and Laboratory Standards Institute (CLSI). For isolation, identification and susceptibility testing of *E. coli* isolates before (day 1) and after treatment (day 9) with moxifloxacin or placebo, stool samples of each patient were cultured on TBX-Chromogen-Agar (Tryptone Bile-X-Glucoronic Agar-SHY, GmbH, Berlin, Germany). After overnight incubation at 37°C, ten individual putative *E. coli* colonies were isolated. Following additional biochemical identification with VITEK2/GN-cards (Biomerieux, INC. Durham, NC 27704, USA) minimal inhibitory concentrations (MICs) of all *E. coli* isolates were determined by microdilution testing according to CLSI standards for ciprofloxacin (MIC ≤1 mg/L susceptible, MIC ≥4 mg/L resistant) and according to the European Committee on Antimicrobial Susceptibility Testing for moxifloxacin (MIC ≤0.5 mg/L susceptible, ≥2 mg/L resistant). *E. coli* isolates were further investigated for the presence of known mutations in the quinolone resistance determining region (QRDR) of the DNA gyrase subunit A gene *gyrA*. The *gyrA* (Ser-83) mutation was detected in isolated DNA by the mismatch amplification mutation assay (MAMA) as described earlier [17]. Expression of human leukocyte antigen-DR (HLA-DR) on monocytes was determined by flow cytometry using a highly standardized quantitative assay as described earlier [18]. Briefly, on days 1, 3, 8, 90, and 180 50 µl of EDTA-blood was stained with 20 µl of monoclonal phycoerythrin-conjugated anti-human leukocyte antigen-DR (HLA-DR) antibodies and peridin chlorophyll (PerCP-Cy5.5)-conjugated anti-CD14-antibodies

(QuantiBrite™, Becton Dickinson) for 30 min in the dark at room temperature. For lysis of erythrocytes, samples were incubated with 500 µl FACS Lysing solution (Becton Dickinson) for 15 min in the dark at room temperature. Subsequently, cells were washed with 1 ml of FACS buffer and analyzed on a FACS Calibur flowcytometer using CellQuest software after QuantiBrite calibration for 1:1 quantification. Final analysis was performed using Quanticale software (all from Becton Dickinson) to obtain the molecules HLA-DR per cell from the measured geometric means. The inter-assay CV was <5% and the inter-lab CV of this assay was <20% [19].

Statistical analysis

Based on a retrospective analysis of infection rates in patients with acute ischemic stroke in the MCA territory treated in the participating centers (data not shown), an infection rate of 40% in the placebo group, and 10% in the group treated with moxifloxacin was assumed. A priori power analysis revealed that a sample size of n = 32 per group was needed (two-sided $\alpha = 5\%$, power 80%). With an estimated drop out rate of 20%, 40 patients per group were needed for enrolment. After enrolment of the last patient a blinded review meeting assessed study patients with respect to protocol violations, which were labelled as "invalid" for per protocol analysis. The efficacy of preventive antibacterial therapy in reducing the incidence of post-stroke infections was investigated using the *per protocol* population as the main analysis set instead of the *intention to treat* approach in this phase IIb trial.

Continuous variables were described using arithmetic mean, standard deviation, and 95% confidence interval (CI) for normally distributed data, or median and range for non-normally distributed data, respectively. Normal distribution was checked by Q-Q-Plots and tested using the modified Kolmogorov-Smirnov test [20]. Absolute and relative frequencies were used for dichotomous variables. The infection rates (and other proportions) of placebo and verum group were compared using Fisher's exact test and the Cochran-Mantel-Haenszel-test, stratified for study centers. For analysis of CRP levels and daily maximum body temperature the multivariate repeated measures analysis of variance was done as described previously [21]. Differences in CRP values between treatment groups were analyzed based on a mixed model of logarithmically transformed data. The parameters day and treatment are assumed fixed, the factor patient is assumed random. Measurements between patients are assumed independent distributed. Within patients a common, otherwise arbitrary covariance matrix is assumed. The following models were used. For the "no interaction model": $\log(CRP_{ikl}) = \mu + \alpha_i + \tau_k + p(\tau)_{l(k)} + \varepsilon_{ikl}$, for the "interaction model": $\log(CRP_{ikl}) = \mu + \alpha_i + \tau_k + \gamma_{ik} + p(\tau)_{l(k)} + \varepsilon_{ikl}$, where μ is the grand mean, α_i the day (i = 1, 2, 3, 4, 5, 6, 7, 9, 11), τ_k the treatment (j = 1 for verum, 2 for placebo), $p(\tau_k)$ the patient nested within treatment, γ_{ik} the interaction treatment by day, and ε_{ikl} the error term. In order to analyse the impact of risk factors for stroke-associated infection multivariately, we used a multivariate logistic regression analysis, including the calculation of odds ratios and the corresponding 95% confidence intervals. Feature selection (in reduction steps) was applied to show the most important influencing (independent) factors. The clinical characteristics of both treatment groups and of patients without and with infection were compared in univariate analyses by Student's t test for continuous variables with a normal distribution. For non-normal data and categorical variables the Mann-Whitney U test and the Chi-Square test for few categories were used, respectively. Survival in treatment and infection groups was calculated according to Kaplan-Meier and compared univariately with Log-Rank-statistics. Multiple tests for differences between the groups in question have been regarded as exploratory ones and were not adjusted for multiplicity. A two-tailed $p<0.05$ was considered statistically significant. The statistical analysis used the Software Package for Social Sciences, SPSS for Windows, 13.0, SPSS, Inc., Chicago, IL and SAS, Version 9.1, by SAS Institute, Inc., Cary, NC, USA.

Results

Study population

Eighty patients with acute ischemic stroke were randomized. For one patient informed consent was withdrawn before receiving study medication. Therefore, 79 patients were included into intention-to-treat (ITT) analysis (verum n = 39; placebo n = 40). Baseline characteristics were similarly matched in both treatment groups (Table 1), except for coronary heart disease which occurred more frequent in the verum group ($p = 0.05$): 66 patients (verum n = 35; placebo n = 31) were analysed *per protocol* (PP). Eight patients, who neither reached the primary endpoint nor completed the study protocol until day 11 had to be excluded from the PP analysis: Four patients (1 verum, 3 placebo) died within 3 days. In three patients, study medication was discontinued due to medical reasons (withdrawal of life supporting therapy, hemicraniectomy, blinding opened due to a suspected CNS infection as the cause of the neurological deficits instead of ischemic stroke). In one patient informed consent was withdrawn. Five additional patients (3 verum, 2 placebo) were retrospectively excluded due to protocol violations (e.g. allocated in infection group while failing predefined infection criteria) and considered "invalid" in the blinded reviewing process (Figure 1).

Primary endpoint: Prevention of post-stroke infections

In the ITT population (n = 79; Table 2A), 19 patients (24.1%) developed infections within 11 days after stroke onset. Six patients (15.4%) treated with moxifloxacin developed an infection as compared with 13 patients (32.5%) in the placebo group (17.1% reduction, Fisher exact: $p = 0.114$; Mantel-Haenszel-test stratified for centres: $p = 0.068$). In PP population (n = 66) infection rate with n = 6 in the moxifloxacin group (17.1%) was significantly lower (Fisher exact: $p = 0.032$; Mantel-Haenszel: $p = 0.033$)

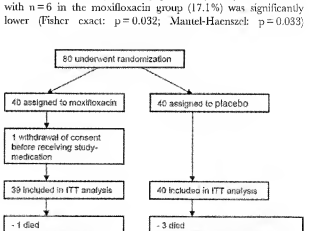

Figure 1. PANTHERIS trial profile.
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Table 1. Baseline characteristics

	Placebo (n = 40)		Verum (n = 39)		p
	n	%	n	%	
Centre 1	25	62.5	22	56.4	0.65
Centre 2	11	27.5	10	25.6	1.00
Centre 3	4	10.0	7	18.0	0.35
Male/female	14/26	35.0/65.0	19/24	38.5/61.5	0.82
Right/left MCA	18/22	45.0/55.0	20/19	51.3/48.7	0.66
Mean age (years) (95%CI)	72.7	68.6–76.9	72.4	68.8–76.1	0.80
NIHSS ad admission (Median,min max)	15	12–25	17	12–21	0.66
Qualifying event					
Cardioembolism	19	47.5	16	41.0	0.65
Atherothrombotic	12	30.0	14	35.9	0.64
Small vessel	2	5.0	1	2.6	1.00
Other	2	5.0	3	7.7	0.66
Unknown	5	12.5	5	12.8	1.00
Risk factors					
Hypertension	24	60.0	27	69.2	0.48
Diabetes mellitus	13	32.5	12	30.8	1.00
Current smoking	6	15.0	3	7.7	0.48
Hypercholesterolaemia	6	15.0	5	12.8	1.00
Atrial fibrillation	16	40.0	11	28.2	0.34
Malignancy	4	10.0	3	7.7	1.00
Coronary heart disease	7	17.5	15	38.5	0.05
Peripheral arterial disease	1	2.5	2	5.1	0.62
COPD	3	7.5	3	7.7	1.00
Prior stroke	5	12.5	4	10.3	1.00
Gastric tube feeding	27	67.5	25	64.1	0.82
Mechanical ventilation	6	15.0	1	2.5	0.11
Urinary catheters	37	92.5	39	100	0.24
Time delay to first dose [h] (mean, 95%CI)	24.0	20.3–27.7	24.0	20.8–27.2	0.70
Baseline parameters	mean	95%CI of mean	mean	95%CI of mean	
Heart rate [beats/min]	81.7	76.2–87.2	77.6	72.4–82.9	0.24
Body temperature [°C]	37.0	36.9–37.2	37.0	36.8–37.2	0.69
Breathing rate, in patients breathing spontaneously [breaths/min]	21.2	18.9–23.5	18.7	16.9–20.6	0.02
Systolic BP [mmHg]	161.6	154.3–168.8	159.0	150.8–167.2	0.55
Diastolic BP[mmHg]	76.8	71.0–82.6	74.5	70.0–79.0	0.54
Glucose [mg/dl]	146.4	130.9–162.0	144.3	129.2–159.3	0.88
C-reactive protein [mg/dl]	1.4	0.8–2.0	0.9	0.5–1.3	0.11
WBC $\times 10^9$/L	9.3	8.3–10.4	9.0	8.0–10.1	0.70

MCA: middle cerebral artery; NIHSS: National Institute of Health Stroke Scale; COPD: chronic obstructive pulmonary disease; BP: blood pressure, WBC: white blood cells.
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compared to the placebo group with 13 patients (41.9%; Table 2B). The reduction of 24.8% (95% CI 2.8% 44.3%) approximates to a number needed to treat (NNT) of 4 (95% CI 2.3–35.3). Treatment with moxifloxacin led to a relative risk reduction of 46.4% in ITT and 59.1% in PP analyses, respectively. A difference in infection rate between both groups emerged between day 2 and 4 and was maintained until day 11 after stroke onset (data not shown). In either population 11 patients suffered from pneumonia (3 verum, 8 placebo) and 8 patients had a urinary tract infection (3 verum, 5 placebo). On average, pneumonia was diagnosed 4.7 days (±2.5) after stroke, and urinary tract infection after 5.2 days (±2.9). In the ITT population the incidence of pneumonia was 8/40 (20.0%) of the placebo group compared with 3/39 (7.7%) of the verum group (12.3% reduction, p = 0.195). In the PP population 8/31 (25.8%) of placebo treated patients suffered from pneumonia, compared to 3/35 (8.6%) of the verum group (reduction 17.2%; p = 0.097). The incidence for urinary tract infections was similar for both treatment groups (ITT: 3/39 (7.7%) verum *vs.* 5/40 (12.5%) placebo; p = 0.712; PP: 3/35 (8.6%) verum *vs.* 5/31 (16.1%) placebo; p = 0.459).

Table 2. Incidence of infections in ITT and PP population

Treatment arm	No infection n [%]	infection n [%]	Sum n
ITT population			
Placebo	27 [67.5]	13 [32.5]	40
Verum	33 [84.6]	6 [15.4]	39
Sum	60 [75.9]	19 [24.1]	79
PP population			
Placebo	18 [58.1]	13 [41.9]	31
Verum	29 [43.9]	6 [17.1]	35
Sum	47 [71.2]	19 [28.8]	66

The numbers and rates [in brackets] of infections in both treatment groups are shown for ITT and PP populations, respectively.

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Bacterial spectrum

Microbiological analysis of microorganisms isolated from patients in the placebo group with infections identified a typical bacterial spectrum of early onset nosocomial pneumonia or urinary tract infection (Table 3). The identification of relevant pathogens was successful in 5 of 11 lower respiratory tract infections and in 4 of 8 urinary tract infections. In the verum group we identified one patient with post-stroke pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Analyzing microbiological isolates obtained from the same patient before starting study medication revealed MRSA colonization.

Analysis of moxifloxacin resistance

We investigated ciprofloxacin and moxifloxacin susceptibility in *E. coli* isolated from stool samples before and after treatment. Before treatment, microbiological analysis of stool samples from 39 patients revealed that 40 patients, 20 in each treatment group, were colonized with *E. coli* (Table 4). Susceptibility testing showed that isolates from 39 patients were susceptible to ciprofloxacin and moxifloxacin. One patient in the placebo group carried a mixed culture of susceptible and resistant *E. coli*. Three days after the end of the treatment period (day 9), stool samples of the same 20 patients of each study group revealed that *E. coli* could be re-isolated from 3 patients of verum group (15%) and from 14 patients of placebo group (70%). Resistant isolates were detected

Table 3. Bacterial pathogens isolated from stroke patients specified for pneumonia and urinary tract infection

Pneumonia (n = 11)	Placebo (n = 8)	Verum (n = 3)
S. aureus (methicillin sensitive)	3	
S. aureus (methicillin resistant)		1
S. pneumoniae	1	
no pathogen	2	2
Not done	2	
Urinary tract infection (n = 8)	**Placebo (n = 5)**	**Verum (n = 3)**
E. coli	1	1
E. coli+*Enterococcus faecalis*	1	
Proteus mirabilis	1	
no pathogen	2	2

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Table 4. Susceptibility analysis of *E. coli* isolates

	E. coli isolates before treatment		*E. coli* isolates after treatment	
Treatment arm	Sensitive[#] n	Resistant[##] n	Sensitive[#] n	Resistant[##] n
Placebo	20	1*	13	1*
Verum	20	0	2	1

[#]ciprofloxacin MIC ≤1 mg/L, moxifloxacin MIC <0.5 mg/L

[##]ciprofloxacin MIC >4 mg/L, moxifloxacin MIC >2 mg/L

*Isolated from a patient carrying a mixture of resistant and sensitive *E. coli* isolates

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in the one patient from the placebo group, who was already initially colonized by resistant *E. coli* (see above) and in one additional patient in the verum group. Genetic analysis by MAMA assay demonstrated that the *gyrA* (Ser-83) mutation was present in resistant *E. coli* isolates but absent in all other susceptible isolates. This indicates that fluoroquinolone resistance in both patients was caused by known molecular changes in the DNA gyrase.

Mechanical ventilation

At study entry no patient was under mechanical ventilation (MV). Within 11 days, seven patients (1 verum, 6 placebo) in the ITT population (Table 1) and five patients (1 verum, 4 placebo) in the PP population underwent MV. Frequencies of MV were not significantly different between both treatment groups (Table 1). Median time point for beginning of MV was at day 3 (range 1–8). The MV of the verum-treated patient started at day 2. This patient developed pneumonia on day five. From the 6 patients of the placebo group which underwent MV (median day 3; range: 1–8) two underwent intubation with clinical signs of pneumonia, and in one patient MV was necessary four days after onset of pneumonia (median day 3, range: 2–4). From the 7 patients undergoing MV two (both from placebo group) died within one month (day 22 and 30).

Daily maximum body temperature and C-reactive protein

Patient maximum body temperature per day did not differ significantly between both treatment groups (ITT population; data not shown). CRP levels from patients (ITT population) of the placebo group increased significantly more than in the verum group ($p = 0{,}0186$; Figure 2). Comparing CRP levels univariately, a significantly lower CRP concentration was found in the verum group at days 3, 5, 6 and 7, which followed the treatment period with an interval of one day (Figure 2).

Survival

To avoid a preselection bias, cumulative survival analyses are based on ITT and not PP population, since patients who died within the first 11 days after stroke without reaching the primary endpoint were considered as 'drop outs' for PP population. Seven (3 verum, 4 placebo) of 79 patients (8.9%) died within 11 days after stroke onset. Within 6 month after stroke 13 (6 verum, 7 placebo) of 72 patients (18.1%) died, and 7 patients were lost in follow-up (3 verum, 4 placebo). Survival did not differ significantly between placebo and verum group 180 days after stroke onset (Log Rank $p = 0.618$, Figure 3). However, cumulative survival of patients with infection compared to patients without infection was significantly different ($p<0.001$) during follow-up period (Figure 4). Patients with stroke-associated pneumonia had a significantly

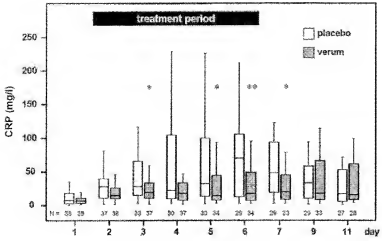

Figure 2. Time course of CRP serum concentration. Time course of CRP levels in placebo and verum group shown by boxplots. Number of patients is indicated by N. CRP levels in the moxifloxacin group are significant lower compared to the placebo group. The p-values for the main effects are <0.0001 for day of CRP measurement and 0.0186 for treatment (multivariate analysis of variance for repeated measurements on logarithmically transformed data, no interaction model). The dependency between treatment and day of CRP measurement has a p-value of 0.0845 (interaction model). In patients of the verum group CRP concentration are significantly lower compared to patients of the placebo group 3, 5, 6, and 7 days after stroke (* $p<0.05$; ** $p<0.005$).
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lower (p = 0.022) survival rate in follow-up compared with patients without infections whereas patients with urinary tract infections showed no differences in cumulative survival compared with patients without infections (p = 0.898, data not shown).

Neurological Outcome

Neurological outcome 6 month after stroke onset was determined by using the Barthel Index (BI) as a measure of limitations in activities of daily living. Comparing both treatment arms after dichotomization, in the ITT population the rate of patients with good outcome (BI≥60) was 64% in the verum group (14 out of 22) compared to 55% in the placebo group (11 out of 20) (p = 0.574). In the PP population the rate of patients with good outcome was 67% in the verum group (14 out of 21) compared to 55% in the placebo group (10 out of 18) (p = 0.483). In ITT as well as PP population, both treatment groups displayed the same median 70 (p = 0.700; p = 0.543). In the ITT population the rate of patients with good outcome was 61% in the non-infection group (20 out of

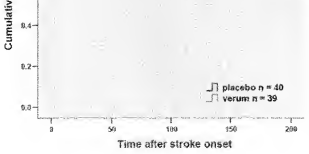

Figure 3. Kaplan-Meier curves of survival in both treatment groups. Crosses indicate time points when patients were lost to follow-up ('censored'; n = 7; verum n = 3, placebo n = 4 placebo). Seven (verum n = 3, placebo n = 4) of 79 patients (8.9%) died within 11 days after stroke onset. Within 6 month after stroke 13 (verum n = 6, placebo n = 7) of 72 patients (18.1%) died.
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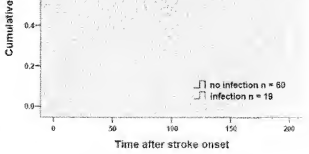

Figure 4. Kaplan-Meier curves of survival in patients with and without infections. Crosses indicate time points when patients were lost to follow-up ('censored'; n = 7, infection n = 1, no infection n = 6). Seven (no infection n = 5, infection n = 2) of 79 patients (8.9%) died within 11 days after stroke onset. Within 6 month after stroke 13 (infection n = 6, no infection n = 7) of 72 patients (18.1%) died.
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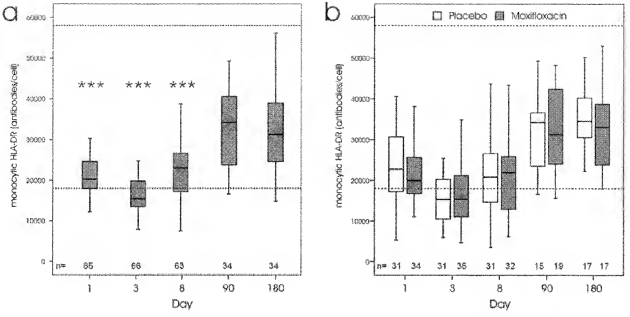

Figure 5. Time course in monocytic HLA-DR expression after stroke. a: Monocytic HLA-DR expression is significantly reduced in all patients at days 1, 3, and 8 compared to 90 and 180 days after stroke (*** $p<0.001$). **b:** The time course of monocytic HLA-DR expression is not significantly different between patients from the placebo and verum groups. Dashed lines indicate the upper and lower reference range for monocytic HLA-DR levels in healthy individuals (5% percentile = 18036 mAb/cell; 95% percentile = 57958 mAb/cell).
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33 patients) compared to 63% in the infection group (5 out of 8, $p = 0.922$). In the PP population the rate of patients with a BI≥60 was 61% in the non-infection group (19 out of 31 patients) compared to 63% in the infection group (5 out of 8, $p = 0.951$).

Levels of monocytic HLA-DR expression

To determine the impact of cerebral ischemia on immune competence in relation to the risk of post-stroke infections we used a novel standardized assay to quantify the expression of monocytic HLA-DR. All patients (PP population) showed signs of post-stroke immunodepression, as indicated by significantly reduced monocytic HLA-DR expression at days 1, 3, and 8 compared to 3 and 6 months after stroke (Figure 5a). There were no significant differences in the time course of monocytic HLA-DR levels between the placebo and verum group (Figure 5b). However, infected patients in the placebo group had significantly lower monocytic HLA-DR levels at days 1, 3, and 8, as shown in Figure 6a. In contrast, no significant differences in monocytic HLA-DR expression were observed between infected and non-infected patients in the verum group at all time points (Figure 6b). Notably, patients without infections in the verum group had significantly lower monocytic HLA-DR levels at day 1 compared to patients without infections in placebo group corroborating that moxifloxacin treatment effectively prevented infections in a proportion of these patients. At 6 month after stroke, monocytic HLA-DR expression returned to normal levels and was not significantly different between surviving patients with and without infections in both groups (Figure 6a, b).

Risk factors of post-stroke infections

Infection rate within 11 days was significantly associated with tube feeding, mechanical ventilation, treatment, and monocytic HLA-DR levels at baseline (day 1 after stroke onset and before study treatment onset) in univariate PP analysis of the placebo group (Table 5). Comparing patients with and without infections of both treatment arms in the PP population (data not shown) only tube feeding was significantly more frequent in infected patients ($p = 0.001$). We performed regression analysis in PP population adjusted for NIHSS at admission, age, tube feeding, mechanical ventilation, monocytic HLA-DR expression at day 1 post stroke and treatment arm, which revealed that treatment arm and the interaction between treatment arm and HLA-DR expression were the strongest independent predictors for post-stroke infections (Table 6).

Adverse events

Table 7 shows types and frequencies of adverse events (AE) in ITT population reported over the whole study period including 6 month follow-up. There were no serious adverse events other than the above reported 19 cases of infections and 12 deaths of patients. Overall 40 cardiovascular, neurological, gastrointestinal, laboratory, and general medical AE were reported. Concerning the frequency of AE both treatment groups did not differ. There was no report of AE related to study medication.

Discussion

PANTHERIS, is an investigator-initiated, multi-center, randomised, double-blind, placebo-controlled trial. PP analysis demonstrates that preventive antibiotic therapy with moxifloxacin within 36 hours after stroke onset reduces infection rate in patients with severe ischemic stroke in the territory of the middle cerebral artery, while ITT analysis revealed only a trend towards beneficial effects for this treatment strategy. Patients in the placebo group were treated according to current treatment guidelines. With respect to antibiotics, they were fully and effectively treated as soon as antibiotic medication was indicated, i.e. as soon as an infection was diagnosed [13,22]. Thus, PP analysis of our proof of principle

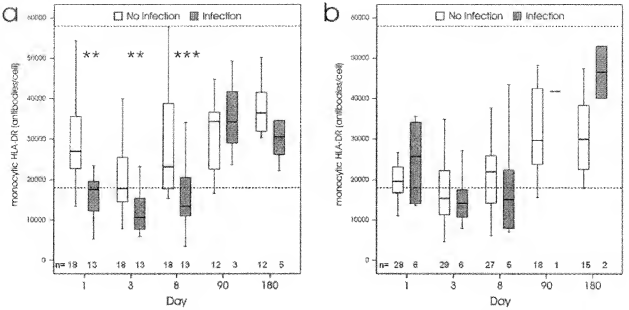

Figure 6. Monocytic HLA-DR expression in patients with and without infections. a: In the placebo group, monocytic HLA-DR expression in patients with infections is significantly reduced compared to patients without infections at day 1 (** $p = 0.003$), 3 (** $p = 0.005$), and 8 (*** $p < 0.001$) days, but not at day 180 after stroke. **b:** In the verum group, monocytic HLA-DR expression is not significantly different between patients with and without infections. Dashed lines indicate the upper and lower reference range for monocytic HLA-DR levels in healthy individuals (5% percentile = 18036 mAb/cell; 95% percentile = 57958 mAb/cell).
doi:10.1371/journal.pone.0002158.g006

trial provides for the first time evidence for a superiority of a preventive anti-infective therapy over current standard therapy.

Up to 95% of patients suffer from at least one relevant complication within the first three months after stroke [1]. Thus, for the majority of stroke patients, general measures targeting early identification and treatment of complications remain the major medical challenge. Complications impair functional and neurological outcome [2,4,8]. Treatment in dedicated stroke units was demonstrated to reduce the incidence of stroke-associated complications [23]. However, even in stroke units, infections after stroke remain common complications with a frequency between 21 and 65% [3]. Among infections, pneumonia have the greatest impact on the neurological outcome and mortality rate after stroke [5,6,8,24]. Pneumonia represents the leading cause of in-hospital mortality of stroke patients, accounting for 31% of all death [8].

Currently, post-stroke pneumonia is thought to be a consequence of aspiration due to dysphagia and immobilization [2,4,25–27]. Forty to 70% of patients develop dysphagia within 3 days after stroke, 40% of them aspirate and approximately one third develop pneumonia [10,28]. As stroke patients with dysphagia are at risk for pneumonia, post-stroke pneumonia is thought to be a preventable complication. Once dysphagia is diagnosed, measures can be taken aimed at prevention of aspiration [28,29]. Feeding tubes are often used to prevent aspiration pneumonia [25,30] but were also identified as the strongest independent predisposing factor for acute post-stroke infections [31]. In the PANTHERIS population, tube feeding is associated with a significantly higher risk of infections, however, it was not an independent risk factor for infections. Results from the large FOOD trials suggest that early tube feeding neither prevents nor favours infection rates [32].

Although post-stroke aspiration increases the risk of developing pneumonia by sevenfold, aspiration alone is not sufficient to explain the high incidence of pneumonia in acute stroke [2,4,25,26,33]. About 50% percent of healthy subjects also aspirate pharyngeal secrets every night to a similar extend as stroke patients, however, without developing pneumonia [34,35]. Thus, our understanding of the high incidence of pneumonia in stroke patients is still incompletely. Since several immune dysfunctions have been reported in patients with acute CNS injury, stroke-induced changes in immunity may explain the high incidence of infections [3,36,37]. In a murine model of cerebral ischemia we provided experimental proof that a neuro-endocrine-mediated systemic immunodepression is an essential cause for a decreased antibacterial defense after acute ischemic stroke leading to post-stroke pneumonia [38]. We further demonstrated that otherwise harmless minor bacterial aspiration leads to severe pneumonia and bacteriemia after ischemic stroke suggesting that the deleterious combination of stroke-induced immunodeficiency with stroke-facilitated aspiration dramatically increases the susceptibility to infection [39]. Results from the PANTHERIS trial provides further evidence for a stroke-induced immunodepression in stroke patients causing post-stroke infections. As marker for immune competency we measured the monocytic HLA-DR expression, which is a well known and sensitive marker for a disturbed immune function in septic and critically ill patients [17,40–42]. Here we describe a significantly reduced monocytic HLA-DR expression in the very early phase after stroke compared to 3 and 6 months after stroke. Remarkably, patients with infections in the placebo, but not verum group had significantly lower monocytic HLA-DR levels at days 1, 3, and 8 compared to non-infected patients. Notably, patients without infections in the verum group had significantly lower monocytic HLA-DR levels at the first day after stroke onset compared to patients without infections in placebo group corroborating that moxifloxacin treatment effectively prevented infections in a proportion of these

Table 5. Univariate analysis for predictors of post-stroke infections in the placebo arm of PP population.

	Infection (N = 13)		No infection (N = 18)		p
	n	%	n	%	
male:female	6/7	46.2/53.8	6/12	33.3/66.7	0.710
Right-left MCA	4/9	30.8/69.2	8/10	44.4/55.6	0.484
Age (95%CI)	75.1	68.5–81.6	70.3	64.9–75.7	0.154
NIHSS 3d admission (Median,min-max)	17	13–25	14.5	12–20	0.080
NIHSS 180 days (Median,min-max)	11.5	4–16	5	1–14	0.108
Qualifying event					
Cardioembolism	8	61.5	7	38.9	0.285
Atherothrombotic	5	38.5	6	33.3	1.000
Small-vessel	0	0.0	1	5.6	1.000
Other	0	0.0	2	11.1	0.497
Unknown	0	0.0	2	11.1	0.497
Risik factors					
Hypertension	7	53.8	13	72.2	0.449
Diabetes mellitus	4	30.8	7	38.9	0.718
Current smoking	3	23.1	2	11.1	0.625
Hypercholesterinemia	3	23.1	2	11.1	0.625
Atrial fibrillation	5	38.5	7	38.9	1.000
Malignoma	1	7.7	2	11.1	1.000
Coronary heart disease	2	15.4	2	11.1	1.000
Peripheral arterial disease	0	0.0	0	0.0	NA
COPD	2	15.4	0	0.0	0.168
Prior Stroke	1	7.7	3	16.7	0.621
Tube feeding	11	84.60	8	44.40	0.032
Urinary catheters	13	100.00	13	83.30	0.245
Mechanical ventilation	4	30.80	0	0.00	0.023
Delay to first dose h (mean, 95%CI)	26.6	19.9–37.3	20.9	16.3–25.3	0.173
Baseline parameters	mean	95%CI of mean	mean	95%CI of mean	
Heart beats [/min]	68.5	75.0–97.9	78.2	70.8–85.6	0.346
Temperature [°C]	37.1	36.9–37.4	36.9	36.6–37.1	0.097
Breathing frequency [/min]	19.4	13.8–24.9	22.4	18.4–26.4	0.472
Systolic BP [mmHg]	166.3	151.1–181.5	159.5	147.4–171.6	0.446
Diastolic BP[mmHg]	82.1	74.4–89.7	76.7	67.8–85.0	0.326
Glucose [mg/dl]	143.6	124.6–162.7	160.3	128.1–192.4	0.781
C-reactive protein [mg/dl]	0.988	0.317–1.659	1.070	0.420–1.720	0.737
WBC $\times 10^9$/L	9.0	7.6–10.4	8.6	7.4–9.8	0.594
mHLA-DR [antib/cell]	17273	12197–22349	28541	23521–33561	0.003

Tube feeding, mechanical ventilation, and expression of mHLA-DR were associated univariately with post-stroke infection.

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patients. Furthermore, reduced monocytic HLA-DR expression at day 1 after stroke and before study treatment onset was a strong independent predictor of subsequent post-stroke infections in the placebo group, but not in the moxifloxacin group. Since there were no significant differences in the time course of monocytic HLA-DR levels between the placebo and verum groups, it is rather unlikely that post-stroke infections by itself cause the reduced HLA-DR expression.

Since the established general measures do not effectively prevent post-stroke infections, and in the light of our pathophysiological concept [36] of post-stroke infections and our preclinical data [38], Preventive Antibacterial Therapy (PAT) warrants further attention as promising new strategy. Using our experimental model of post-stroke infections, we have demonstrated that post-stroke infections can effectively be reduced by preventive antibiotic therapy with moxifloxacin. More importantly, in this stroke model moxifloxacin not only prevents the development of infections and fever, it also significantly reduces mortality, and improves neurological outcome [11]. Consequently, the primary endpoint of the PANTHERIS trial aimed at preventing severe stroke-associated infections, in particular pneumonia. Based on a retrospective analysis of stroke patients in participating stroke units infections arise between 2 and 7 days after stroke onset (data not shown). In order to cover this critical time period effectively, in

Table 6. Logistic regression analysis of independent predictors for post-stroke infections

Effect	Parameter estimation			Standard	p-value
	Estimate	95% Confidence Interval		error	
		Lower	Upper		
Model					
Treatment					0.015
Interaction: treatment and HLA-DR					0.038
Estimates					
Intercept	−12.7	−38.4	13.1	13.1	0.336
Treatment	47.2	9.0879	85.4014	19.5	0.015
HLA-DR level in verum arm	1.113	−1.4563	3.6827	1.311	0.396
HLA-DR level in placebo arm	−3.507	−6.3319	−0.6822	1.441	0.015

Shown are the nominal p-values and estimates for the parameters remaining in the model after backward selection. Factors and covariates included for selection were: NIHSS at admission, age, tube feeding, mechanical ventilation, HLA-DR expression (Day 1), treatment, and interaction between treatment and HLA-DR (Day 1) expression. The final logistic model was: $\log(p/1\text{-}p) = \mu + \text{treatment} + \theta_{\text{treatment}} \log(\text{HLA-DR})$; p: number of infected patients within 11 days/total number of patients (in the respective treatment group).

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PANTHERIS treatment was started 9 to 36 hours after stroke onset and continued for 5 days. In order to ensure that preventive antibacterial therapy not only shifts infections to a later time point infection rate was studied within 11 days post stroke. In the per protocol analysis, PANTHERIS demonstrated the efficacy of preventive anti-infective therapy with moxifloxacin. Compared to an infection rate of 41.9% in the standard therapy (placebo) group, only 17.1% of verum treated patients suffered from infections. Further evidence for the efficacy of preventive anti-infective therapy is the significant reduction of C-reactive protein in the moxifloxacin treated group, compared with placebo. Of all infections, predominantly pneumonia seems to be prevented, although this difference did not reach statistic significance. Mechanical ventilation, a known strong risk factor for nosocomial pneumonia [43], appeared to be more frequent in placebo compared to moxifloxacin group, again without reaching statistical significance level. Although we cannot exclude an inclusion bias, it would seem rather unlikely that the higher pneumonia rate in the placebo group should be caused by the higher frequency of mechanical ventilation in this group. On the contrary, since pneumonia preceded mechanical ventilation in the placebo-treated patient, our data suggest that PAT might reduce the need for mechanical ventilation in patients with acute stroke.

Stroke-associated infections lead to poor outcome [3], however the support for an independent causal relationship between infections and poor neurological outcome was recently challenged [37]. The PANTHERIS trial confirms that infections are associated with a significantly reduced survival rate. However, we remained short of demonstrating that patients treated with moxifloxacin should have improved clinical outcome or increased survival rate at 6 months after stroke, compared with patients treated according to current standards. These results seem to support the conclusion that stroke-associated infections are not the cause but rather a marker for a poor neurological outcome following stroke. However, since PANTHERIS was not sufficiently powered to address this issue, it remains open whether post-stroke infections lead to a worse outcome in stroke or not.

Chamorro and co-workers were the first to investigate in a randomized, placebo-controlled, double-blind trial the effect of preventive antibiotic therapy in stroke [44]. Their single-center ESPIAS trial included 136 patients using levofloxacin in a dose of 500 mg/d for 3 days starting within 24 hours after stroke onset.

Table 7. Safety analysis

	Placebo (n = 40)		Verum (n = 39)		
	n	%	n	%	p
1 AE	14	35	9	22.5	0.32
≥2 AE	2	5	5	12.5	0.43
Pulmonary	3	7.5	0	0	0.24
Dyspnoea	2	5	0	0	
Pneumothorax	1	2.5	0	0	
Neurological	4	10	8	20.5	0.23
Increased intracranial pressure	2	5	2	5.1	
Hemorrhagic transformation of stroke	1	2.5	2	5.1	
Seizures	1	2.5	1	2.6	
Recurrent stroke	0	0	1	2.6	
Frontal lobe syndrome	0	0	1	2.6	
Hallucination	0	0	1	2.6	
Cardiac arrhythmia	1	2.5	1	2.6	1
Ventricular tachycardia	1	2.5	0	0	
Sinus bradycardia	0	0	1	2.6	
Gastrointestinal	4	10	3	7.7	1
Abdominal pain	1	2.5	0	0	
Diarrhea	2	5	2	5.1	
Nausea/Vomitting	1	2.5	1	2.6	
Laboratory changes	2	5	4	10.3	0.43
Hypothyreosis	1	2.5	0	0	
Hyponatriaemia	1	2.5	0	0	
Alanine aminotransferase increased	0	0	1	2.6	
Blood creatine phosphokinase increased	0	0	1	2.6	
Haemoglobin decreased	0	0	1	2.6	
Hypocalcaemia	0	0	1	2.6	
Other	1	2.5	3	7.7	0.36
Arthralgia	0	0	2	5.1	
Hemolysis	0	0	1	2.6	
Pharyngeal bleeding	1	2.5	0	0	

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Based on an interim futility analysis, ESPIAS was prematurely stopped since levofloxacin neither prevented post-stroke infections nor improved outcome in patients with ischemic or hemorrhagic stroke. ESPIAS even suggested a non-significant rise of mortality rate in the verum group. Although both trials are similar in design, several differences may explain the discordant results. For example, in ESPIAS patients were treated sooner but shorter after stroke onset compared to PANTHERIS. Since the majority of stroke-associated infections occur within five days after stroke onset [33,45,46], the longer treatment period in PANTHERIS may be a crucial advantage covering this critical time period. Furthermore, in PANTHERIS moxifloxacin was chosen for its superior effect against aerobic pathogens [47], as local epidemiological data of stroke patients (unpublished data) demonstrated a predominating Gram positive spectrum (*Streptococcus pneumoniae, Staphylococcus aureus*) in pneumonia with a low incidence of moxifloxacin resistant pathogens such as MRSA and *Pseudomonas aeruginosa*. In addition, *in vitro* antibacterial activity of moxifloxacin against anaerobes is superior compared to levofloxacin [48], which might be of relevance, since anaerobic pathogens need consideration in aspiration pneumonia [49].

A major drawback of preventive antibiotic therapy is the potential induction of antibiotic resistance. The observation that susceptible *E. coli* isolates from one patient became resistant during moxifloxacin treatment indicates selection of fluoroquinolone-resistant bacteria by preventive treatment with moxifloxacin. However, the low *E. coli* re-isolation rate of 15% among patients treated with moxifloxacin (as compared to 70% in the placebo group) suggests moxifloxacin affects normal gut flora and was effective enough to eradicate *E. coli* in 17 out of 20 patients. The fact that in six patients of the placebo group, *E. coli* could not be re-isolated after treatment suggests that the intestinal *E. coli* populations were not solely affected by moxifloxacin treatment.

In conclusion, PP analysis of PANTHERIS suggests that preventive antibiotic therapy with moxifloxacin reduces the infection rate in patients with severe ischemic stroke in the MCA territory. Since PANTHERIS as proof of concept trial was not designed to demonstrate clinical superiority of preventive antibacterial treatment in a routine environment and ITT analysis revealed only a trend towards beneficial effects of preventive antiinfective treatment caution is needed. Analyses of secondary endpoints demonstratc a significant lower survival rate during 6 month follow-up for patients with infections. Even though infection rate was reduced in patients treated with moxifloxacin, survival and neurological outcome were not significantly improved compared to placebo. PANTHERIS provides the framework of data for our current planning of a phase III trial to further investigate the innovative concept of preventive antibacterial therapy in stroke patients focussing on effectiveness rather than efficacy. If post-stroke infections are independent risk factors for poor outcome and if they can be effectively prevented, there will be an urgent need for predicting factors of post-stroke infections. Indicators of immunodepression such as monocytic HLA-DR expression may be interesting candidate markers to identify patients at high risk for infectious complications, which warrant further confirmation in prospective trials.

Supporting Information

Protocol S1 Trial Protocol
Found at: doi:10.1371/journal.pone.0002158.s001 (3.93 MB PDF)

CONSORT S1 Checklist S1
Found at: doi:10.1371/journal.pone.0002158.s002 (0.05 MB DOC)

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Author Contributions

Conceived and designed the experiments: UD AM HH KP KW TW GA UG. Performed the experiments: SB AM HH KP CM JK WR CD EH. Analyzed the data: KW. Contributed reagents/materials/analysis tools: SB EH. Wrote the paper: AM HH JG. Other: Added contributions: CM SB KW EH UD KP. Added comments: WR CD VG TW GA HV JK.

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